The Campaign Against Microbes

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THE CAMPAIGN AGAINST MICROBES

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PREFACE.

THE studies collected in this book have not been grouped together at random. They relate to different types of infectious disorders, and are fairly representative of the problems and methods of experimental medicine. The series might be entitled : *The objects of laboratory research at the present day, for the prosecution of the anti-microbe campaign.*

The longest chapter is devoted to cancer, a subject which is still veiled in obscurity, though familiar to all students of vital phenomena, whether medical men, histologists, bacteriologists, chemists, or specialists in hygiene. If it be true that in science "the known loses its attraction, while the unknown is ever full of charm" (Claude Bernard), this is indeed the problem that must excite the keenest interest. Everything connected with it is mysterious—the nature of the disease, its origin, and its causes ; we have scarcely begun to approach it by the experimental method. We are indeed at the starting point of the chase, and the prize is far away : imagine a study on tuberculosis written about 1875, or on rabies about 1880. Gropings such as these, such diversity of opinions and tendencies, such haphazard experiments represent science itself in travail.

Tuberculosis is the typical chronic microbic disease, an attack of which renders the organism *susceptible* instead of vaccinating it. We are well acquainted with the natural history of the tubercle bacillus, as the result of the very large number of memoirs that have appeared subsequently to the discoveries of Robert Koch. The malady itself, however, has hitherto failed to yield to any of the methods of scientific therapeutics, vaccination, and serum-therapy, which have proved so successful in the case of other diseases. At the moment of writing,

indeed, we have to record the failure of von Behring's *bovo-vaccination*, from which great things had been expected.

In the case of sleeping sickness we are dealing with a tropical disease the peculiarities of which are of a novel character; that is to say, the protozoon that causes it, the fly by which it is propagated, and the chemical treatment that holds out a promise of cure.

Tetanus and diphtheria are types of *toxic* disease which it is possible to reproduce by means of the poison of the microbe in the absence of the microbe itself, the remedy for which has been found in the shape of antitoxic serum, and with regard to which a difficult problem still presents itself—namely, after the curative remedy to discover a prophylactic. From the scientific point of view, there is nothing of greater educational value than the story of the tetanus investigations: on the one hand, we have a series of enigmas which had to be solved one after the other; and, on the other, a succession of experiments which remain lessons and models.

The chapter on enteritis and the intestinal microbes will perhaps give some idea of the extensive researches upon the intestinal flora, in which Metchnikoff has been so ardent a pioneer. The originality of the problem lies not so much in the technique, which is that of classical microbiology, as in the immensity of the horizons that this bold spirit has revealed to us. The question at issue is the perfecting or renovation of the human species by a carefully considered system of nutrition, and by the scientific selection of the races of microbes of which we are the hosts. It is the A B C of hygiene, which should retard the approach of old age, and assure to mankind the normal cycle of life. Here, however, we cannot do more than refer the reader to the "Études sur la nature humaine" and the "Essais optimistes" of the illustrious biologist.

Although more than a hundred years have elapsed since the date of Jenner's magnificent discovery, we are still ignorant of the nature of the virus of small-pox and vaccine, and a series of infections referable to the same type has been described. The result is that there is not a chapter of more present interest than that which appears to belong solely to history.

It would have been easy to combine the two studies on cancer, which were written at an interval of a few months, as

also the two on tuberculosis. By leaving them distinct, it has been possible to show how a question may develop in the space of a year. To be present at one of those great discoveries that, like the rising sun, illuminate a domain which was dark the night before is not a matter of everyday occurrence. Besides sudden developments, there are the imperceptible advances by which the slow transformations are brought about. The change is visible from day to day only to those who follow very closely the patient labour of the investigators. From one year to another it is perceptible to the whole world. Hundreds of workers bring up their grain of sand and the edifice is built. Between the month of March, 1905, and October, 1906, there were published at least a thousand memoirs on Schaudinn's spirillum. A German author, on bringing before the scientific world a work on tuberculosis written some ten years previously, found himself confronted with eleven thousand publications which had appeared in the interval. The industry of scientists resembles that of ants.

I make no pretence to a definite philosophy, but would rather steer clear of anything of the kind. What is the use of wearying the reader and of preventing him from thinking, in his own way, what he is capable of thinking as well as I ? If the simple narration of facts and experiments suggests some reflections on the experimental method, or the co-efficient of certainty or uncertainty of ideas and results, I have left these to be read between the lines. I have no more claim to be a scientific critic than to be a philosopher, remembering as I do the saying of Claude Bernard : "I do not admit the possibility of there being in science men whose speciality is criticism, as there are in letters and the arts. In each science criticism must be pronounced by the scientists themselves. . . ." My sole qualification is that I have been permitted to labour in the great scientific workshop, and to participate in the investigations that I describe, which is the only method of following them.

At the present day it is the fashion to "popularize" science. The phrase would be unpleasant, were it implied that science could become "vulgar" as well as popular, and that it is necessary to degrade or alter it in order to render it accessible. There is but one truth for everyone, and we have no right to disseminate partial truths. So far from being of an inferior

quality, an elementary book should display greater clearness, method, and precision.

Science occupies too large a place in life for us not to respond to the taste of the public, which desires to know its beauty and utility. On the other hand, there is room for a certain amount of scepticism as to how much science it is possible to communicate to minds (even the best) unfamiliar with laboratory research. What is to be done? Excessive simplification and unnecessary detail must alike be avoided. To popularize is to select. The rule is in the technical portion to pass over all that is devoid of educational value ; to explain what is essential in terms which professional scientists would not repudiate ; to present science as liberal and humane ; to aim at something higher than the immediate interest of curiosity, and to offer to those whom their occupations keep at a distance from scientific work sound ideas as to the place and power of man in Nature. To popularize science would be labour in vain if, besides its instructive value, such work did not possess the merit of contributing to the general progress by cultivating the mind.

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CAMPAIGN AGAINST MICROBES.

CANCER.

I.

PUBLIC attention and interest have long been monopolized by tuberculosis, and every eye followed the brilliant rocket sent up by von Behring. Even in his fear of disease and death man is exclusive and follows the fashion. Nevertheless, the propaganda against tuberculosis has brought about the collaboration of the laboratories, private initiative, and public powers, and prepared the campaign against another enemy. Cancer is a worthy ally of tuberculosis ; the one is the special foe of the young ; the other attacks mature lives in full bearing, which represent society's greatest capital in the shape of work and energy.

At the present time we are beginning to speak of cancer apart from special media. The sensational discovery has not yet been made, but it will come. As the result of a long series of investigations, a development has taken place in the laboratory phase of the subject, and the latter has now arrived at the decisive moment when a problem passes from the region of pure observation into that of experiment. The study of cancer is approximately at the stage at which tuberculosis was when that disease was shown by Villemin to be contagious and inoculable. Since Villemin we have had Pasteur, whose labours have endowed science with fresh powers, by which the cancer investigations will profit. First, however, it is necessary to win over a sovereign auxiliary—the powerfully interested sympathy of the public.

Cancer, the name bestowed by popular imagination upon

this strange malady, signifies a beast fastened upon and gnawing its prey.

The tissues of which our organs are composed are assemblages of cells ; the cells forming a tissue are of the same kind, and every organ is composed of definite and constant tissues. A layman, on being shown such a structure, would be impressed by the order of the whole, and order is one of the vital laws. Look at the profile of a bridge with its arches ; the blocks forming the abutments and spans are hewn and arranged symmetrically, while above are rough stones placed side by side, the hollows and angles of which dovetail one into the other. If a minute vertical section of our epidermis be examined under the microscope, the same regularity and methodical arrangement will be found. Let us imagine a piece of ground honeycombed with a multitude of wells almost touching one another ; if we think of the stones with which the cavities of these wells are regularly lined, and then suppose the whole arrangement to be reduced to an infinitely small scale, we have the mucous membrane of the stomach, with the ducts and glands which bore their way into it, and the cylindrical cells with which these canals and glands are lined. Take a bunch of grapes and imagine the skin of each berry to be thicker and composed of a layer of cells pressed one against the other like the cells in a honeycomb, or the cavities in a pomegranate ; then imagine that the stalk of each berry is a tiny duct, which opens into a more important canal, and that the stem of the bunch is the collecting duct. Here we have a representation of a gland, and if we imagine an enormous number of simple glands, heaped one against the other and kept together by a supporting tissue, we have a glandular organ, such as a breast, liver, or kidney. These organs, skin, mucous membrane lining the digestive tract, and glands, if studied in a healthy condition, are the same in individuals of the same species. Old age may shrivel up the constituent elements, but it will not disturb the general arrangement.

One day, from an unknown cause, these microcosms are thrown into disorder. A cell or a group of cells commences to multiply and proliferate in an unusual manner, and the mass thus formed forces back the healthy tissue around it. When this mass has become perceptible to the eye or touch, the

doctor diagnoses a tumour, though he cannot tell how long a time has elapsed since it arose within the organ. If its structure be examined under the microscope, the elements of the healthy tissues will be found to be still more or less recognizable, but anarchy may be said to have arisen in the community, and everything is in confusion. To such a degree have the stones and blocks begun to multiply, that the floor of the bridge has grown thicker; such a disturbance has set in among the cells lining the wells that wells and glands are encumbered and obstructed with superfluous cells, to such an extent that they can no longer perform their functions. Nay, more: the cells have become deformed and have assumed a uniform aspect, which is that of the cancer cell; the result is a tumour.

Certain tumours remain stationary and cause no great mischief; they are troublesome, but not fatal, and, like a bump or a large parasite, they are borne and endured; such tumours are said to be benign. If they are too troublesome, they are removed, and do not recur. There are, however, "malignant" tumours, which are not permanently restricted to the place in which they originated. Suppose we have a nodule formed in the mucous membrane of the stomach; sooner or later, in an altogether different organ, as for instance in the liver or the lung, there appears a secondary nodule which under the microscope exhibits the structure, not of the liver or lung, but of the stomach, the original seat of the malady. The fact is that diseased or cancer cells have emigrated from the original tumour and started a colony elsewhere; traces of their passage will be met with in the lymphatics or blood-vessels. The purely local tumour is serious enough, but that which spreads and proliferates to a distance is worse; we may operate on the stem, but it is impossible to extirpate the shoots.

Such is the second characteristic of malignant tumours or cancers; they set up in different organs these secondary tumours, which are called *metastases*. The malady therefore, at first localized at one spot and then disseminated hither and thither, becomes a generalized affection; the patient's strength declines; the symptoms are those of an infectious disease, an intoxication and a wasting away which has been termed cancerous phthisis. The final stages of cancer are almost those of an infectious disease. Attempts to find a cause for the disease

or to discover a microbe have been without avail, or such discoveries as have been reported have led to nothing, for this malady is unlike any other. In tuberculosis, in actinomycosis, and in leprosy there are formed many nodules, which are also masses of cells or small tumours. In these cases, however, the cells are those that have been mobilized for the purpose of seizing, arresting, surrounding, and devouring a microbe which had penetrated into the organism; and the marauding microbe is found in the midst of the police-cells, which have faithfully performed their appointed task. The disorder is of a salutary kind; it is like a street disturbance, which is quickly repressed. To revert to our similes of the bridge, wells, and bunch of grapes, it is a repairing process, a cleft stopped, a consolidation, a cicatrix. In a cancer we have cells and nothing but cells, which refuse to explain why they have left their places, and have much less the air of policemen than the suspicious demeanour of vagabonds.

It is not surprising that it should have been said at the outset that "the culprit is simply the cell. A cancer is produced by cells in revolt, in delirium, in a state of anarchy. Moreover, in the case of living beings, we are well acquainted with this power of indefinite reproduction and multiplication on the part of a given cell, which is a normal phenomenon at the commencement of life. When the tiny organism is engaged in rapid growth, its cells multiply with a similar energy, which is very necessary for the building up of tissues and organs. When the organism becomes adult, this ardour calms down; construction no longer takes place, and maintenance is all that is necessary. But if, this time crazy and purposeless, the former activity reawakes at a certain point, disorder disturbs the definitive structure, and we have the commencement of a cancer."

Cancer then was at first considered to be a malady of cellular origin, the active agent in which was believed to be the cell itself; on this hypothesis it would differ fundamentally from the infectious diseases, in which the cells react to the attack of an invading microbe, but do not become active by themselves. This power of boundless multiplication possessed by the cancer cell would therefore, in the adult, be merely the return of the energies formerly possessed by the cell at the time of embryonic life. There is, say the supporters of the

cell-theory, nothing to warrant the hypothesis of a microbe, which besides is unnecessary; in cancer the only virus is the cell. Given a cell capable of multiplying—which is one of the definitions of its life—but which does so out of season, we have the germ of cancer. There is nothing here which savours of an infectious and contagious disorder.

This seductive idea has assumed several forms, and been expressed in as many theories. The conservation in the adult of a group of cells, the energy of which becomes dormant and subsequently reawakes without visible cause, is the celebrated theory of Cohnheim. As for other scientists, it is considered by Thiersch and Waldeyer that there is no necessity to assume the existence of these relics of embryonic life, since they hold that the power of multiplication possessed by cells at all ages provides a sufficient explanation. In the normal condition, however, the epithelial cells, which are the important elements in our mucous membranes and glands, are packed in and supported by connective tissue, which limits their growth. Should this counterpoise be removed the fount of life bubbles over; the cells multiply, and we have a tumour. In Ribbert's opinion the cells forming a glandular or cutaneous layer are rivals, which limit and contain one another; if a rupture takes place in the series disorder sets in; like ill-disciplined soldiers, the cells break their ranks, and form abnormal tissues, that is to say, a cancer. In all these conceptions, however, the fundamental idea is the same: the invasion of normal tissues by cancer cells is an invasion of barbarians. To such an extent is the invading and devastating impulse inherent in them that it sometimes happens that, in the same individual, two neighbouring cancerous nodules invade one another. Like a veritable band of anarchists, the members of which prey upon one another, within one and the same cancer cells are seen to devour their fellows, by a sort of monstrous phagocytosis.

These theories may explain the anatomical aspect of cancers, but they do not account for the metastases and infecting action. Why is it that some of these remains of embryonic cells, or some of these cases of recurrence of embryonic energy, are not found in all species of animals? Why has no case of cancer ever been seen among the millions of guinea-pigs that have passed through our laboratories? Why does rupture of

equilibrium take place between tissues, and why does it occur in a single tissue ? How is hereditary cancer to be explained—is it a fact or a myth ? Why should the grandfather be attacked in the stomach, his daughter in the breast, and his grandson in the skin ; and what is the reason of many other facts unknown to the theorists of former days ?

Let us forget for a while this idea of the cell being diseased and forming the causative factor in disease ; we shall meet with it again. Let us cultivate an open mind, free from theories, and go back some ten or fifteen years in order to retrace the path followed by observers and experimenters, and to collect facts which shall really be facts.

From the earliest times popular opinion, with its anonymous and wonderful powers of observation, has regarded the two diseases, tuberculosis and cancer, as contagious. True or false, this belief made its way into certain legislative enactments, and in the Prussian Sanitary Ordinance of 1797 we find cancer included among contagious diseases. At the present day surgeons, who are well acquainted with cancer, and whose practice has extended over several generations, are under the impression that cancer, like tuberculosis, is becoming more and more common. They have also noticed that certain regions provide their hospitals with more patients than others, as though they were cancer countries. The question, therefore, arises whether cancer is an endemic or an epidemic disease. The problem is a medical one, and also one for statisticians, who have devoted themselves to it. In England and in Germany, at great expense and by means of specially arranged schedules, either on the occasion of a national census or by special investigations, the attempt has been made to obtain a return of those suffering from cancer. The figures have confirmed the impression of the surgeons, and an increase in the frequency of cancer has everywhere been found.

Statistics, if not precisely accommodating, are always elastic, and their aid has been sought to enforce different conclusions. Those who think that cancer is spontaneous in its origin and those who believe it to be contagious have had recourse to statistics for arguments, and sometimes too much has been asked from them, for it is necessary to arrange and examine them with a critical mind. The investigation by Gastpar and

Weinberg, dealing with the town of Stuttgart, may be taken as a model. Conclusions are drawn from the figures as to the heredity of cancer, the influence of age, profession, surroundings, whether town or country, of sex, social condition, marriage or celibacy, maternity or sterility, poverty or wealth. . . . The answers on so many special points could not be categorical, but all the evidence agrees as the extension of the disease.

According to Barker, in New York, in a million inhabitants, there were 400 deaths from cancer in 1875, and 530 in 1885. In England, 7,245 cases were recorded in 1861, and 17,113 in 1887. In London the average of deaths from cancer has risen as follows: 0·42 (1851-1860); 0·68 (1881); 0·83 (1895); 0·99 (1902). The indications yielded by the figures for the Netherlands, Prussia, and Paris are similar.

Investigations that, instead of embracing millions of inhabitants, are confined to a single locality, yield more precise results. A geographical study of cancer of this kind seeks to discover the relations between the disease and a given soil, climate, habitation, or diet. Now there are cancer districts, cancer villages, cancer streets, and cancer houses. The frequency of cancer of the lip in the French Cevennes is well known. In a certain village in Normandy, out of a total of 74 deaths in seven years, 11, or 15 per cent., were due to cancer. According to the register of a hospital at Jena, 1,455 cancer patients were sent in by 785 parishes, while 339 of these were furnished by 7 parishes.

In the course of a medical practice extending over twenty-two years, Dr. Robert Behla made a minute study of the cases of cancer in his town, Luckau, in Prussia, not far from Berlin. Luckau is a small town of about 5,000 inhabitants, surrounded by a moat filled with water, with two suburbs, Sandow and Kalau, each of which has perhaps a thousand inhabitants. The death-rate from cancer is very high there (a ninth of the total mortality, instead of 2 per cent., as in the rest of Prussia), and very unequally distributed; in the suburb of Kalau it amounts to 15 per cent. There is above all one street in this suburb, the *Gartengasse*, or Garden Lane, almost all the houses in which have had at least one cancer patient, and in which a certain house has alone had three or four in a period of eighteen years. It is the lowest and dampest part of the town; sunken gardens lie behind the houses; the inhabitants consume

large quantities of vegetables, which are watered with water not derived from springs, and are more or less well washed. The humidity of the locality and the vegetable diet are alone incriminated by Dr. Behla, who was one of the first to suggest that cancer comes from the soil.

Conditions in Upper Bavaria have been made the subject of a similar study by Dr. Kolb, of Munich, who arrives at the conclusion that cancer is rare on virgin and on permeable soils, but more frequent on impermeable soils, alluvial ground, clays, and all damp soils. He adopts the hypothesis of a cancer microbe, which he supposes to exist in the superficial layers of the soil, and to be transmitted by water, vegetables, dust, and even the earth of wine-cellars, which is carried into living-rooms on the soles of boots.

In the village in Normandy to which reference has already been made, there have been cases of cancer in seventeen houses out of fifty-four; in another village in the same province there have been three cases in five years in one house. In this instance a young woman died from cancer in the abdomen; five years later her father died from cancer of the intestine, and her mother shortly afterwards from cancer of the stomach. Mention is made of a house of good appearance at Lyons, situated on the banks of the Saône, in which, in 1873, there was a case of cancer of the stomach on the first floor, a similar case in the porter's lodge in 1875, a third case on the entresol in 1877, and a case of cancer of the parotid gland on the second floor in 1882. In Great Britain, Mr. Shattock quotes a house with four cases in fourteen years, among persons who, like the patients in the house at Lyons, did not belong to the same family. Winter Blyth mentions a room in which three successive lodgers were attacked, while a lady friend, who frequently visited one of them, was attacked in her turn. At Glasgow, A. Scott quotes a workmen's dwelling, damp though clean, in which three successive inmates, all of whom were night watchmen, died of cancer, the second two years after the first; the third eighteen months after the second.

These facts savour of contagion; they do not indicate heredity. We know that a similar illusion has obtained in the case of tuberculosis, which was long believed to be hereditary, without proof. After the discovery of the bacillus

and the modes of contagion, it was recognized that heredity is but a disguised form of the latter. The germ does not pass from the parents to the offspring, but from the parents to the house, to the surrounding medium, and thence to the child; it is capable of passing equally well from the child to the parents. As regards cancer, the odds are ten to one that the theory of heredity is a myth, which will vanish before the demonstration of its contagiousness. It is devoutly to be wished that this may prove to be so, since against heredity nothing can be done, while to fight contagion we have science and hygiene.

The geography of cancer has led to and already made popular the idea of a cancer microbe, still unknown, living in the earth, and especially in damp soils, and doubtless only somewhat rarely finding the conditions favourable to its transmission to man. Behla supposed that it might come from plants and trees, by the agency of insects, especially wasps. It has been said that damp villages, situated near woods, are frequently contaminated, and it has even been stated that the trees bear tumours transmissible to man, of which the woodcutters make pastry. . . . Fiction bulks largely in all this. What is indisputable is an endemicity, which is explicable only by assuming the agency of a microbe; that the latter should live in the soil, the reservoir of all such organisms, is not surprising.

Then began the era of experiments, for the first of which Nature itself was responsible. It was remarked by surgeons that cancer of the lip commences with the lower lip, and that the upper one subsequently becomes involved, there being a process of auto-inoculation. They also observed that an operation is sometimes followed by recurrence on the line of incision, as though, in spite of the apparent perfection of the aseptic precautions, operative inoculation had taken place. Since experiments upon human beings are impossible, these spontaneous results were all that could be obtained. When a disease is peculiar to man, experiments are out of the question, science is at a standstill, and despondency takes the place of hope. Fortunately for us, cancer is not the special prerogative of man. It is found in cattle, dogs, horses, sheep, and pigs; it occurs in the fowl, and has been seen in a

rhinoceros, while cases of it have been observed in carp and lizards. It is, however, in white mice that cancer is best known, and it may be that these animals will prove the deliverers of mankind.

Under the white fur of one of these pretty little animals there sometimes appears a nodule, which, after developing rapidly, ulcerates, and causes death. This is a cancer identical in structure with cancer in man; we find the same anarchy among the cells, the same metastases, and the same withering away at the end. Just as among human beings there are cancer districts, streets, and houses, so among mice there are strains and cages in which the same phenomenon occurs. These facts are perfectly well established, since white mice are in great demand in laboratories, and considerable attention is devoted to breeding them. Strains of mice are known in which there has never been a single case of cancer, while some other strain may produce two, four, or six such cases in a year, although to prove that the disease is contagious is not easy. If the over-eager or over-hasty investigator has the infected cage brought to the laboratory, it is vain to continue breeding under conditions apparently identical. The change of surroundings has suppressed one unknown but necessary factor, and the contagion is arrested.

A few years ago, a young scientist named Morau, who was working at the Faculty of Medicine in Paris, having a cancerous mouse in his hands, conceived the idea of operating upon it, and of using a crushed fragment of the tumour for the inoculation of other mice. By so doing Morau laid the foundation of the experimental study of cancer in mice, which was subsequently developed by Jensen at Copenhagen, by Borrel at the Pasteur Institute in Paris, and by Ehrlich in Germany.

Just as there are different kinds of cancer in man, so there are in the mouse—sarcoma of the jaw, lymphoma, and carcinoma—and the tumour studied by Jensen was not the same as that investigated by Borrel. Both are specific, and transmissible only from mouse to mouse; on other species of animals they have no effect. The results are even somewhat unequal in the case of different varieties of mouse, and these tumours take less well in grey than in white mice. When investigators exchanged their mice for the purpose of com-

parative study, they found that Copenhagen cancer takes more rarely in mice from Berlin, London, and Paris, than in Danish mice. Thus, while Jensen was able to transmit his type of tumour, from mouse to mouse, through twenty-three generations, with 20 per cent. to 40 per cent. of successes, Bashford, in London, only obtained five cancerous mice out of 259 mice inoculated ; it is possible that the virus had been injured by the voyage, since in subsequent inoculations the proportion of successes increased, though without reaching the result attained in Copenhagen. Borrel obtained on an average 10 per cent. of successful inoculations ; the first time that inoculations were made from the same tumour in London, out of seventy-eight cases there was but a single success.

It has been proved beyond dispute that daughter tumours, when reinoculated, produce fresh tumours identical with the originals. To use a laboratory expression, they are inoculable in series. It has been calculated by Dr. Bashford, of London, who has performed about ten thousand inoculations on mice, that a single tumour, by dint of serial transmission, produced, in three and a half years, a mass of tumours equivalent to 1,500 adult mice, which in bulk would equal a giant mouse as large as a St. Bernard dog.

A very large number of inoculations has been made by Professor Ehrlich, of Frankfort, starting with seventy-one cancerous mice. In certain cases the daughter tumour was late in arising and very slow in development ; weeks and months were spent in waiting for the appearance of a nodule perceptible to the touch. In certain other cases, however, growth was extraordinarily rapid. Virulence was increased by the passage from mouse to mouse, and the inoculations regularly gave 80 per cent. of successes. A week after inoculation, the young tumour already weighed 2 grammes, a heavy weight for a mouse of some 15 grammes ; at the end of three weeks the tumour weighed 3 grammes ; perhaps the reader will try to imagine a man with a tumour weighing 33 lb. ! In two months the mouse had developed a cancer as large as itself. The essential signs of the malignity of the cancer are seen in this ultra-rapid growth, and this extreme energy in multiplication on the part of the cancer cells.

The comparison with a St. Bernard dog is no longer of any

avail. To estimate the mass of cancer that can be produced from a tumour so easy to inoculate and so rapid in growth that sixty generations are obtained in one year, Ehrlich and Apolant have recourse to very simple calculations, which yield some fantastic figures. Nothing is easier than to inoculate fifteen mice with equal parts of a single tumour ; in a week's time the initial volume has become multiplied by 10, and at the end of each successive week a fresh multiplication by 10 is observable. Thus, at the end of four weeks we have a mass ten thousand times greater than the original tumour. Supposing that we started with a cancer of the size of a cubic centimetre and weighing about a gramme, in a year's time, that is to say, in sixty generations, it would be possible to have produced a cancerous mass equal to 10^{60} cubic centimetres. This volume is that of a cube having a side measuring 1,000 milliard kilometres, or of a sphere the diameter of which would be 890 million times, and the volume 7×10^{26} times that of the sun !

In the course of his experiments, Ehrlich noticed a fact of extreme importance, namely, the transformation of a tumour inoculated in series. In the case to which we are referring there was a carcinoma, or glandular cancer, which remained carcinoma for ten generations ; among the cell components of the carcinoma there then appeared those of a sarcoma, which is a cancer of a totally different type. By the fourteenth generation the tumour became a pure sarcoma, reinoculable with 90 per cent. of success, and so rapid in growth that the space of a fortnight was all that was necessary to obtain a cancer as large as a cherry. These facts admit of no doubt ; a scientist like Ehrlich speaks with authority, and the same metamorphosis has been observed by the American investigator Leo Loeb. The study of cancer is now pursued by the experimental method.

Are we, then, as regards cancer, at the point to which Villemin brought us in the case of tuberculosis ? Cancer is inoculable by means of a particle of cancer, just as tuberculosis was found to be inoculable by means of a particle of tubercle. Cancer has had its Villemin ; it awaits the discovery of the microbe ; it awaits its Robert Koch. . . . We must not, however, allow ourselves to be enslaved by this analogy, since the facts do not warrant so simple a conclusion. We set out

with the idea of a cell as the causative agent, and met with that of a microbe by the way. Let us not yet say, "It is the one or the other." Suppose it were both!

It is now our turn to suffer the criticisms of those who do not admit that cancer is an infectious disease. This is no sport of theorists. It is the method of research that is at stake, and success depends upon it.

These so-called inoculations, we are told, are not inoculations, but transplantations. When, after the manner of Villemin, a fresh animal is inoculated with a fragment of tuberculous tissue, if the fate of the introduced cells in the inoculated organism be followed, it is seen that they do not go far. They are destroyed, absorbed, and devoured by phagocytes; that which lives and multiplies is the bacillus inoculated at the same time as they. A different state of things is discovered on following the fate of the inoculated cancer cells; while in the former case the cells shrivel up and disappear, the latter continue to live, multiply, and form the new tumour. It is rather a graft than an inoculation in the strict sense of the word, and these successful grafts account for the invading and infecting properties of cancer, and for these metastases that there is so much anxiety to explain. Metastasis occurs when that which is performed experimentally from mouse to mouse takes place from one tissue to another, in the same cancerous subject—it is an auto-transplantation.

If the tubercle to be inoculated be crushed in a mortar as finely as you please, the inoculation will be infallibly successful, because the crushing process, which destroys the cells, does not kill the bacilli. Crush the particle of cancer, however, and the inoculation fails. If we filter through gauze or through coarse paper the juice obtained by crushing tubercle, the bacilli pass through the meshes of the gauze or the pores in the paper, and the filtrate is infectious. But filter the cancer pulp in the same way, and the result will be absolute failure.

It is therefore the cell that is the parasite. Give us a cell with these aberrations in its energy, with this power of untimely multiplication, and we will produce for you a cancer, a species of bastard organism, a parasite, which sponges on the host upon which it is implanted, which lives longer than this host, and is capable of living for ten, twenty, or a hundred

years perhaps (whereas the individual mouse lives for three), which destroys, one after another, the series of hosts in which it exists.

As a final and most decisive argument, we are asked to point out the cancer microbe.

Some ten years ago, it was observed by Mallassez and his pupils that certain protozoa, known as coccidia, are capable of producing, in the intestine or liver of the animals in which they are parasitic, abnormal multiplication of the epithelial cells, or so-called "adenomata," which are benign tumours. The idea suggested itself that these protozoa might be types of micro-organisms capable of causing cells to proliferate. This daring and highly scientific hypothesis was inevitable, and, like every well-founded hypothesis, excited a fever of research. Seductive forms were seen under the microscope, but the new knowledge acquired from day to day in studying coccidia showed that the supposed presence of these organisms in cancer was an illusion. A long training in microscopical research is necessary in order to account for errors of this kind, supported as they are by so strong an air of probability. These investigations possessed the merit of thoroughly exploring a path by which it was known that there would be no return. Neither the coccidia, nor the yeasts to which they have given place, are the microbes of cancer, and the investigators who are the firmest believers in the cancer microbe have ceased to believe in the former organisms.

An inoculation with cancer is, doubtless, not the same thing as an inoculation with tubercular tissue, but all the same the former is something more than a mere graft. Experimental grafts have been made by physiologists, and grafts for therapeutic purposes are made by surgeons every day ; these grafts however, do not infect an organism. We are told that a metastasis is an auto-transplantation, and the term may be allowed to pass, but we should much like to know what it is that sets the cells in motion, and renders them infectious.

The pseudo-parasites of cancer have had their day, and we, who apparently stood so much in need of them, have thrown them overboard. We have no need of these yeasts and coccidia in order to explain a pathological multiplication of epithelial cells. Borrel has made a very close study of authentic examples

of virus possessing this property, which can be isolated and even seen. The diseases produced by these matters have so pronounced a family resemblance, that he has grouped them together under the term *epithelioses.* Cow-pox and small-pox are virulent and contagious diseases ; now, the virus of each produces, in the viscera or on the skin, small tumours, or pustules, which are aggregations of proliferated cells. Analogous pustules are produced on the skin and in the internal organs by the rot, or pox, of the sheep and goat. Neither the virus of sheep-pox, nor that of cow-pox, nor that of small-pox has yet been seen, but there is a whole category of such matters, the existence of which cannot be denied, although no one has yet seen them. These are the "invisible microbes," an unfortunate term, since those by whom they have been discovered do not accept it, at least in its literal sense. They are not invisible microbes, but microbes which have not been seen, whether because the staining process that would render them visible has not yet been found out, or because they are extremely minute, or on account of both reasons at once. The virus of sheep-pox, for instance, is minute enough to pass through the pores of Chamberland candles, which might be used to filter drinking water, and do not permit the passage of microbes such as the typhus bacillus ; so that, without seeing it, it is possible to isolate it by filtration, and to inoculate it in a state of purity. With a cubic centimetre of the transparent liquid in which the virus is present though invisible, a million animals can be infected. The juice of mouse-cancer has been filtered, and the filtrate was not virulent, but the experiments in this case left much to be desired. It may be that the crushing was not sufficiently thorough, and if the microbe should live in the interior of the cell, it might not be altogether easy to extract.

In pigeons there are sometimes found, on the eyelids and in the angles of the beak, small epithelial tumours, which are highly contagious and so similar to the pustules caused by vaccination, that the disease is called "pigeon-pox," just as rot is sheep-pox. In the case of the tumours on the pigeon, however, the microbe is visible—to those who know how to see it. In the diseased cell, when crushed between two slips of glass and examined under the microscope, there is to be observed a kind of opaque ball, which was also at one time

regarded as a protozoan parasite. Borrel has shown that this globule is resolvable into extremely minute granules, which are undoubtedly microbes of very small size.

In these tumours on the pigeon the microbe is intracellular, and numerous observations tend to show that the case is the same with regard to the virus, as yet unseen, of cow-pox and small-pox. Search the cell and the virus will be found. The probabilities are all in favour of its being the same in cancer. Hitherto cancer has not been inoculated without inoculating the cancer cell; but why is the cell infectious? It is so because it is infected: it is not virus, but a virus-carrier. Its virulence is that of a small culture tube or culture sac, and this observation is of the highest importance in the science of infectious diseases.

The cancer cell owes its properties to the fact that it harbours in its interior, in its protoplasm, or it may even be in its nucleus, a microbe which, for its part, perhaps finds favourable conditions of existence only in the substance of a living cell. This is a new illustration of the symbiosis described by M. Le Dantec in a paper entitled "La Tuberculose et les affections chroniques."[1] The author in question mentioned the classical examples of lichens formed by fungi and algæ, and of the Paramecium filled with zoochlorellæ. The vegetable kingdom furnishes other instances of the same kind, which possess the greater interest for us since they are cases of cellular symbiosis, in which the individual cell suffers little, while the organism as a whole is somewhat severely affected. As illustrations, we may mention the disease of the leaves of wheat known as rust, and the affection of cabbages, in which the cells of the roots, infected with *Plasmodiophora*, react by multiplying, forming curious tumours, which are highly contagious.

Yet how much more true is this idea of a symbiosis with regard to cancer than to tuberculosis! In the case of the latter disease, cell and microbe from the very first day do all that they can to destroy one another. The one has its poison, and the other its ferments, and there is a duel to the death. Though, with regard to the organism as a whole, the disease

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[1] *Revue de Paris*, October 15, 1905.

may be long and run a chronic course, it seems short enough in the case of the cell. In cancer the cell undergoes modifications in structure, which are the clearest indications of adaptation; it becomes a new species of cell. "Symbiosis perfect and yet injurious, to the whole organism just as much as to the symbiotic elements themselves," says Le Dantec of tuberculosis. I would say of cancer: Symbiosis still more perfect, and much more injurious, or more rapidly injurious to the organism as a whole than to the symbiotic elements themselves.

A microbe in possession of or lodging in a comfortable cell must find itself very badly off when removed from it. It is not inured to hardships, as are the microbes that wander about in the blood or actually take up their abode among the cells. Intracellular virus has little power of resistance; the virulence of Jensen's mouse tumour is destroyed by forty-eight hours' sojourn in a stove, or even by semi-desiccation, and inoculations are thoroughly successful only when perfectly fresh cells are used. How are we to reconcile this frailness with the facts of contagion? In order to pass from the soil to man—if indeed it comes from the soil—or from one human being to another, the microbe has to go through a trying change of surroundings, and runs a great risk of being overtaken *en route* by light, heat, or desiccation, which are fatal to it. Is contagion possible without this passage through the open?

There is nothing to prove that the transit takes place in the open; it may be that the microbe accomplishes it without quitting the closed cell. In some cases virus changes its quarters under comfortable conditions; it gets itself carried by living creatures, which might easily transport a cell fully charged with virulent matter. The plague bacillus has little power of resistance, and is hardly capable of surviving in water or in the soil. To enable it to pass from one patient to another, the agency of the flea is often of service to it; the flea sucks the virus from a plague-stricken rat, and then inoculates another rat or a human being. The trypanosome, or microbe of sleeping sickness, in order to pass from one human being to another, has need of the services of a fly, and of a particular species of fly and no other. The microbe of malaria is dependent upon the mosquito, and even remains in the insect

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long enough to pass through in its stomach metamorphoses which it would not pass through in any mosquito other than the accredited Anopheles. Who knows whether the cancer microbe, an eccentric and exacting recluse, does not require the assistance of an insect, which is at once a go-between and a receiver ?

One fact is beyond dispute ; all the mice found by Borrel to be suffering from spontaneous cancer of the mammary or cutaneous glands were peculiarly infested with acari, minute creatures of almost microscopic size. Looked at from a distance, there is nothing in this. But at close quarters, under the microscope or the lens, with its mandibles, hooked claws, and distended abdomen, the creature appears perfectly capable of creeping into and attaching itself to the tiniest folds of skin, and of penetrating into the orifices of the excretory ducts of the glands, which are open doors leading into the depths of the tissues. From the relations existing between cancer and the soil there is reason to suspect the parasitic worms, which make their way into the alimentary canal in water, vegetables, salads, and uncooked fruit. These parasites may themselves be carriers of various other parasitic organisms, and such an association of parasites bodes no good. Borrel has observed, in certain tumours in mice and in nodules of cancer in human beings, suspicious traces such as would indicate the passage of one of these hosts, perhaps a carrier of the anonymous virus. These parasites are engaged in passing from the alimentary canal to the liver or lung by way of the lymph and the blood, in piercing the vessels, and in forcing their way through tissues and cells ; more than one example of this is known in pathology. There is, perhaps more than one enemy ; if the evil were brought home to a worm, it would not necessarily be a reason for absolving an acarus from blame. Several types of cancer exist, and since the situations are so varied there is probably more than one mode of transmission.

The field of research is boundless, and the task of discovering the cause of this strange disease may well engage the united efforts of medical men, zoologists, and microbiologists. To recapitulate what has already been stated, we have in cancer—infectious cells, which cannot be so unless they are themselves infected ; a virus which, in all probability, origin-

ates in the soil, which lives in a state of symbiosis with the parasitically affected cells, and, in order to circulate naturally among living beings, needs a carrier to protect its frailness ; a disease caused by diseased cells, the weak point in which appears to be an exuberance of disordered vitality ; a living creature perishing because an unknown virus stirs up in its tissues energies comparable to those which build up the tissues and organs of the embryo ; finally, as indeed is the case in every disease, death caused by a mysterious play of the forces that constitute life.

The reader will doubtless imagine that all the resources of hygiene and science must surely have been arrayed against an evil which spares neither beggars nor kings. Let us see what has been attempted in different countries, the comparison is instructive.

In Germany, under the auspices of the Emperor, and under the direction of the most distinguished scientists and doctors, a "Society for the Study of Cancer" (Die Komitee für Krebsforschung) was founded in 1900 ; it possesses a special review, and a clinic at the Berlin University has been specially appropriated to cancer patients. In the Prussian Budget of 1902-3 there was included for the foundation of this clinic a sum equal to £4,800. To the central institution are attached other institutions in the States composing the German Empire, including : a section of the Frankfort Imperial Institute of Experimental Therapeutics, under the direction of Professor Ehrlich ; a special hospital at Ludwigsburg ; a society in Bavaria for the study of the disease, founded in 1905 at Munich, and modelled on the one in Berlin ; a society established at Stuttgart in 1903, for Würtemberg ; an institute at Heidelberg, due to private generosity and under the direction of Professor Czerny ; and another at Carlsruhe, for the Grand Duchy of Baden. We see, therefore, that Germany is not entirely given up to sanatoria.

In Hungary, there is a central society for research ; in Portugal, there is a commission attached to the ministry of the interior, and a research laboratory ; in Greece, a society for the study of the disease. At Moscow, there is a clinic, a hospital, and a laboratory specially devoted to cancer patients, the whole forming an institute which was opened in

1903, with an endowment of £48,000, provided by the Morosoff family and certain other donors.

In England there is the Cancer Research Fund, established under the patronage of His Majesty the King, and under the Presidency of the Prince of Wales; the Vice-Presidents are Lord Lister, Lord Strathcona and Mount Royal, and Messrs. A. J. Balfour, H. L. Bischoffsheim, J. Werner, and W. Waldorf Astor. Everything that may concern the study of cancer, throughout the immense extent of the British Empire, with its metropolis and colonies, is officially centralized in London, in the laboratory controlled by Dr. Bashford. There is also in London, at the Middlesex Hospital, a special section for cancer patients, with a research laboratory; this foundation alone represents an expenditure of £20,000 sterling.

In America, in the State of New York, there is the special laboratory at Buffalo, with an annual expenditure of about £4,000, and the Huntington Fund for Cancer Research; while to the University of Harvard there is attached the Caroline Brewer Croft Cancer Commission.

The Germans have realized that, at the present day, science, like war, is a matter of numbers and masses, and they are attacking the problem with their customary method and discipline. The English well know how to deal with matters of importance, and are organizing the campaign against cancer accordingly. In America people are endeavouring to outdo one another in unstinted generosity.

In France nothing is being done. Some fifteen years ago a committee was formed under the presidency of Dr. Verneuil, but this committee never met. The eminent surgeon who presided over it is dead, and his place has not been filled. There is no special clinic, no special hospital, and no special laboratory. Good-will, however exists, and we have isolated talent. Facts, observations, and experiments, which are of primary importance in science, are scattered and to a large extent lost, and public opinion has still to be won over. Yet France is the country of Pasteur.

II.

A public opinion on the subject of cancer does at last exist. It is nowadays a widespread and even popular belief that the disease is becoming more and more common, that it is probably infectious and endemic, and perhaps contagious; and that heredity, diet, and domicile may play a part in it. The discussions of to-day are by no means unlike those of Villemin's time on the origin of tuberculosis; some day or other a skilful and successful investigator will discover the microbe of cancer.

At last there has been founded in Paris a society for the study of the disease, affiliated to the foreign societies and to the international committee, which sits in Berlin.

It is useless to ask whether there is any good in acquainting an impatient public with the phases of a research which demands patience above everything. Public opinion, once it is awakened from an indifference solely due to ignorance, is extremely sensitive, and imagination and sentiment amplify the ideas of heredity and contagion. Doubtless there are those who believe themselves doomed because they were born of cancerous parents, and uneasy souls who imagine that cancer is contagious like measles, while others, because there has been much talk of "*cancer houses*," mistrust the family home. Where does the truth lie? What ought we to fear, and what ought we to do? In order to give a definite answer, we must understand the cause of cancer, and this we do not yet know. But since there is nothing that causes so much alarm as idle fancies, there is much to be gained by reviewing the facts and theories and submitting them to a little criticism.

A demand is made upon statistics for information as to the increase or decrease in the number of cases of cancer; as to its relation to age; as to the influence of sex, profession, diet, domicile, marriage, and heredity. It will be seen that these questions cover a very wide field.

Here to begin with are some round figures, extracted from the general statistics published in each country. Per million inhabitants, there were registered in Italy 519 deaths from cancer in 1899; in Prussia, 520 (1897); in Ireland, 579 (1897); Norway, 632 (1893); Austria, 680 (1897); Scotland, 770 (1897); Saxony, 840 (1897); Sweden, 850 (1894); Holland, 880 (1896);

Switzerland, 1,324 (1898) ; New York, 628 (1890) ; Paris, 1,180 (1897) ; Berlin, 1,537 (men) and 1,775 (women), in 1895.[1] On comparing years separated by a considerable interval, it is seen that cancer has increased, often to an alarming degree.

	1880	1888	1900
England — Whole country	511	621	829
England — London	587	696	940
Austria (Cisleithan)	376	491	739
Bavaria	562	—	985
Scotland — Whole country	491	610	770
Scotland — Chief towns	465	628	880
France (Paris)	982	1,071	1,210
Holland	501	690	959
Ireland	343	430	580
Italy	211	427	519
Norway	430	540	850
Prussia	261	409	573
Switzerland	—	1,144	1,324
Baltimore	—	451	608
Buffalo	320	—	520
Washington	600	694	703
State of Massachusetts	520	600	606

According to Payne, the increase was, in Ireland, from 1880 to 1897, 27 per cent. ; in England, from 1851 to 1890, 24 per cent. for the portion of the population between the ages of 25 and 35 ; 55 per cent. for that between the ages of 35 and 45 ; and for that between 45 and 55 years of age, 80 per cent. An insurance society at Gotha lost through cancer, per million lives insured, 1,430 persons in 1875, and 2,360 in 1899. At Helsingfors, in 3,775 autopsies, from 1868 to 1888, there were 5 per cent. of cancer cases for the years 1868-78, and 10 per cent. for the years 1878-88. From statistics recently published by Saul (Berlin), it appears that in Prussia the mortality from cancer, from 1895 to 1904, increased by 49 per cent., while in the same period the population showed an increase of only 17 per cent.

Round figures may be eloquent, but they show very little. All of them are liable, if not to dispute, at least to differences of interpretation. By what system of returns are they obtained, and by what kind of staff, administrative or medical, are they

[1] Figures given by De Bovis (*Semaine médicale*, September 10-24, 1902), per million inhabitants.

calculated? How, and with what coefficient of certitude was the diagnosis made — by simple clinical examination, after operation, or by microscopical examination? There is no great interest in stating the number of cases of cancer as compared with the total population; we must divide the population into classes according to age, and say, so many deaths between 30 and 40, so many between 40 and 50, &c. De Bovis, King and Newsholme, and Andrew maintain that the increase in frequency is only apparent, and that it is explained by the insufficiency of the old statistics, increased longevity, and the progress in clinical medicine. It is impossible to draw any conclusions from round figures.[1]

More instructive are the statistics relating to a definite group of human beings, which extend over a fairly large number of years, include details as to age, sex, profession, social condition, and the organ attacked, and are comparable among themselves because they are drawn up according to the same rules. Such statistics are not yet very numerous, and are unequal in value. Two remarks may be made with reference to the columns of figures already prepared: firstly, that there are questions to which they may supply answers, and others as to which they give scarcely any information; secondly, that the answers are more vague in proportion as the statistics have been better drawn up, and that, on certain points at least, decided answers are derived from rough statistics, which resemble a gross return.

Juliusberger has made use of the documents (extending over fifteen years, from 1885 to 1889) of the Friedrich-Wilhelm Life and Accident Insurance Society, of Berlin, which has a double *clientèle*—the wealthier class (life assurances) and the working-classes (insurances against accidents).[2] He has compiled the

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[1] "When we see," wrote Œsterlen, "that the proportion of deaths from cancer to the living population is annually 1 per 900 at Geneva, 1 per 2,900 in England, 1 per 2,400 in London, and to the total number of deaths, 1 in 20 at Geneva, 1 in 65 in England, and 1 in 55 in London; and when we reflect that the malady with which we are dealing is one of the most constantly fatal of all diseases, we are justified in suspecting, as regards England for instance, the completeness of the returns. It is impossible to affirm with certainty that any disease is increasing or decreasing; so how can we draw from this, conclusions as to the cause?" (*Handbuch der medizinischen Statistik*, 1865.)

[2] *Zeitschrift für Krebsforschung*, Bd. iii., p. 106.

fullest possible information with reference to the 7,081 cases of cancer, with which the registers of the society provided him, and the answers that he gives us are more definite. Is cancer becoming more common? Yes; among those who are comfortably off, the increase in fifteen years was from 6·9 to 9·5 per cent. in men, and from 13·3 to 15·3 per cent. in women; among the working-class, from 3·7 to 8 per cent. (men), and from 11·4 to 12·9 per cent. (women). Is it true that cancer is more common among women, especially in the mercantile middle class? Yes; but this difference to the disadvantage of women is on the decrease. Are we to believe in heredity? Yes, but the proofs are not very strong (note that the period embraced by the statistics is only fifteen years, and therefore would hardly include the data necessary for following the history of families). What is the influence of profession or occupation? This is difficult to determine in the case of women; in that of men of the middle class, out of 484 deaths there were 120 employees and minor officials (24·79 per cent.), 79 tradesmen (16·32 per cent.), 26 professors and teachers, 23 hotel keepers, and 10 "property-owners"; then come a few officers, doctors, and ecclesiastics. . . . In the working-class, day labourers (*Tagearbeiter*) in the towns furnish 34·76 per cent., and those in the country 8·55 per cent., or together 43·31 per cent.; shoemakers, 4·60 per cent.; masons, 4·052 per cent.; gardeners, 1·45 per cent.; all this, however, has no great scientific value.[1] What are the organs most frequently attacked? They are as follows: stomach, 40 per cent.; female organs of generation, 30 per cent.; breast, 5 per cent.; liver, 9 per cent.; intestine, 6 per cent.; œsophagus, 5 per cent.; larynx, 1·5 per cent.; tongue, 1 per cent.; thyroid gland, 0·5 per cent.; lungs, 0·6 per cent. . . In short, we find that the alimentary canal and the organs connected therewith are especially subject to cancer. All statistics and all observations point to this conclusion, which is the most definite and the easiest to establish.

In 1904, Weinberg and Gastpar published some statistics as

[1] According to statistics published by Aschoff (for the years 1897-99), the following list shows the incidence of cancer in relation to occupation, arranged in order of increasing frequency: workers at chemical products, metal and machinery workers, those engaged in textile industries and the fabrication of wearing apparel, workers at foodstuffs, *lastly, those who devote themselves to gardening, work in the forests, and agriculture.*

to cancer at Stuttgart from 1873 to 1902.[1] This is a model of what such a return should be, though the answers are often evasive. The documents utilized are death certificates (*Totenscheine*), family registers, an institution peculiar to Würtemberg, dating from 1808 ; papers of information and sets of questions filled up by the doctors of the districts from their notes and recollections ; address books, useful for determining professions and domiciles ; the municipal statistics of lodgings, kept by a muncipal medical officer ; the registers of the Royal Statisical Office ; and statements sent in by surgeons as to the operations performed by them (useful for calculating, besides the mortality, the ratio of incidence in the community). The authors took great pains to guard themselves against the causes of error inherent in all work of this nature. They know the objections that are usually raised : the population is shifting ; even in the non-industrial towns, a third of the inhabitants each year removes to other streets or to the country ; a patient suffering from cancer is usually ill for several years ; can such a patient be traced? What can be proved as to heredity, unless it is possible to go back fifty or sixty years, and prepare genealogical trees like that of the Rougon-Macquart family?

The answers, which afford a very good idea of what can be obtained by this method, vary in probability or certainty according to the questions. The great frequency of cancer of the alimentary tract is indisputable—827 per 1,000 in men ; in women, per 1,000 tumours, we find 496 of the digestive organs, 272 of the organs of generation, and 105 of the breast. The frequency of cancer increases with time and with age, as shown by the following table, which gives the numbers per million inhabitants :—

	Men	Women
1873-82	411	866
1883-92	526	909
1893-1902	733	1,009

The details are as follows :—

	Digestive tract		Stomach		Liver		Other digestive organs		Breast		Organs of generation	
	M.	W.	M.	W.	M.	W.	M.	W.	M.	W.	M.	W.
1873-82	262	294	149	183	48	63	65	48	4	93	0	244
1883-92	349	390	176	244	57	65	116	81	2	87	0	297
1893-1902	532	473	256	265	80	95	196	113	11	03	7	261

[1] *Zeitschrift für Krebsforschung*, Bd. ii., p. 195.

Generally speaking, cancer is on the increase, particularly in men, and especially as regards the digestive tract. In women, on the other hand, it would rather appear that the opposite is the case, particularly as regards the organs of generation ; the same observation has been made in Berlin, Hamburg, Frankfort-on-the-Main, and Dundee ; it is, perhaps, to be attributed to the progress in hygiene. To enter into details, however, it is possible that the increase of the disease in men is merely apparent, and to be explained by the extension of surgical and medical treatment, and the progress in diagnosis. In the same way it is possible that the diminution of cancer in women is likewise only apparent, and to be explained by earlier diagnosis and operation, especially in cases of cancer of the breast.

Among men, those who are married would appear to be attacked more frequently than bachelors ; married women would seem to suffer from cancer of the generative organs more often than those who are single, while cancer of the breast is apparently more common in unmarried women. In the latter situation the disease appears to occur less often in women who have had several children than in those who have had none. It cannot be said that maternity is conducive to cancer of the generative organs in woman. Nothing definite can be said as to the influence of social position ; the organs of generation would appear to be more frequently attacked in the case of women of the poorer classes ; these women have more children, but in their case child-birth takes place under conditions less satisfactory from a medical point of view. To the question whether rich or poor pay the heavier tribute, no answer can be given. In the case of married couples, it does not appear from our statistics that cancer is transmissible from one to the other ; and as to the influence of heredity, no conclusion can be drawn. With respect to the question whether cancer is of more common occurrence in the country or in towns, local statistics indicate that mortality is higher in rural districts, while it has been stoutly maintained that the disease is more common among urban populations. This is not really so, however ; it is well known that town patients, especially surgical cases, are sent into the country ; also that urban populations are not divided up in the same way as rural ones. In Berlin, for example, in 1895, 66 per cent. of the inhabitants were more than 20 years old,

whereas in the whole of Prussia only 45 per cent. were of this age. It is true that people are less long-lived in towns, but diagnoses are more thoroughly performed there. It will be observed that the factors in the case are mutually compensatory, and it will be seen to how large an extent the figures are subject to discussion.

We must not expect statistics, which are far from being perfect, to supply scientific information, but only orientations. They enable us to deduce from the facts a *tendency* more significant than the crude figures. A table of statistics is far from being equal in value to the well-founded impression of a surgeon, who has been in practice for even ten years ; in the opinion of any such practitioner the increase of cancer is beyond doubt. Again, the element of solid fact in statistics has no meaning unless the quantitative are completed by the addition of qualitative data, and, by the side of the figures, there be recorded, in the column for observations, remarks on the conditions as to individual and social hygiene, and on the circumstances of the patient with regard to habitat, district, soil, and house. Statistics are but the most abstract element in a concrete study, which is continually developing, and may be termed the *geography of cancer*.

Cancer does not occur with equal frequency in all countries. Nowhere in Europe is it so prevalent as in Switzerland (North-eastern Cantons), especially the Canton of Lucerne.[1] It is almost as prevalent, however, in certain districts of the Grand Duchy of Baden, Würtemberg, and Bavaria ; less common in Switzerland in the Italian than in the German Cantons ; in Italy, less common in the south than in the north. In France it was long ago pointed out that cancer occurs with greatest frequency in the departments of the north and east (Aisne, Ardennes), the Cévennes (cancer of the lip), and certain districts near Lyons, while the disease is much more rare in Brittany and the Mediterranean basin.

Since the work of Haviland and Nason in England, suspicion has fallen upon alluvial soils, the valleys of slow-flowing water courses, and humid regions in general. I have already cited the treatise by Dr. Kolb,[2] of Munich, who has made a

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[1] Nencki, *Journal de Statistique suisse*, 1900.

[2] "Der Einfluss von Boden u. Haus auf die Häufigkeit des Krebses, nach Detail-Untersuchungen in Bayern." Munich, 1904.

complete study of the soil and subsoil of Upper Bavaria. He describes a great zone of cancer, which extends to the north of the Alpine chain, from Vienna to Geneva, and includes the less favoured Swiss Cantons ; the area in question consists of Tertiary formations, ground sodden with fresh water, alluvial soils, and regions formerly gouged out deeply by enormous glaciers ; the annual rainfall is heavy (from $31\frac{1}{2}$ in. to nearly 67 in.). Cancer is much more common on impermeable than on permeable strata. What is the action of the soil ? There is but one hypothesis that is in accordance with the diversity of circumstances : the soil acts through its humidity. The composition of the rocks, the extent of forests and grass lands, act only as factors in the production of humidity. At Passau, there has been noted during a series of years an almost constant parallelism between the amount of the annual rainfall and the cancer curve.

These geological observations provide a scientific basis for the monographs that can be written on some particular province, town, or village, and Kolb's work contains admirable detailed surveys of the cancer geography of the towns in Upper Bavaria.

Many writers have referred to the example afforded by the town of Luckau, in Prussia, which has been so well studied, from the same point of view, by Dr. Behla, a medical man who has practised there for some thirty years, and is a staunch upholder of the view that cancer is endemic. Luckau is a small town of 5,000 inhabitants, surrounded by a ditch, which receives the sewage and dirty water ; the water from the ditch, which is stagnant, fœtid in summer, and extremely rich in all kinds of microbes, is frequently used for watering the gardens, which are especially devoted to the raising of vegetables for the market. The town possesses two suburbs, each of which contains about 1,000 inhabitants, and consists of a fairly long street with a few by-streets opening into it. The western suburb, called Sandow, lies higher than the other, and its subsoil is sand. Kalau, the eastern suburb, occupies a lower situation, with a clayey and much damper subsoil, and many gardens. Now Luckau is a "cancer town," and it is in Kalau, the damper part, that most of the cases occur. The total number of cases from 1888 to 1897 amounted to 63, 35 of which belonged to Kalau, 23 to the central part of the town

(3,800 inhabitants) and 5 to Sandow ; this gives 1 death in 20 from cancer at Luckau, and 1 in 6 at Kalau, while in Prussia, according to the statistics for the years 1887-1896, the rate is only 1 in 40. From 1878 to 1887 the figures were : total 68—34 for Kalau, 31 for the central town, and 3 for Sandow. There were 10 cases in 1898, and 12 in 1899 ; of these 22 cases, 12 occurred in Kalau and 10 in the central part of the town ; the cancer death-rate was 1 in 8. From 1852 to 1877 (25 years) there were 31 cases, and from 1877 to 1899 (22 years) 81 cases ; the increase is manifest. On a plan of the town the houses in which the deaths took place have been indicated by a mark ; in certain houses there have been as many as 5 deaths, while in others there has not been a single one.[1] We therefore have "cancer towns," and in these towns "cancer houses."

The example afforded by Luckau is far from being an exception, and as regards Germany mention has been made of Grossbringen, near Weimar, Rehburg, and Grafenhagen (in Pomerania). A German doctor relates that in a hospital for surgical cases at Greifswald, on the arrival of a patient suffering from cancer, the senior surgeon remarked : "Of course, it is another case from Darss !" (a neighbouring village). At Saint-Claude, in France, there is a great difference in the death-rate from cancer between the upper and the lower portion of the town. Dr. Foucault, in his study on Fontainebleau, lays the blame on humidity.[2] As other illustrations of the same kind may be mentioned : Carmarouche, in marshy country ; Huntingdon, in England ; the island of Norderney, in the North Sea (in twenty years twenty-two cases, in the south-eastern and damper portion of the island, as opposed to nine in the north-western portion) ; the south of Scotland, and examples by the dozen in Kolb's book on Upper Bavaria.

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[1] R. Behla, "Die Erkrankungen der Stadt Luckau," *Zeitschrift für Medizinalbeamte*, 1901.

[2] *Bulletin de l'Académie de Médecine*, May 31, 1904 : "A fact which has struck me is that the more low-lying and damper the neighbourhood happens to be, the greater is the mortality from cancer. . . . Almost all the houses in which several cases of cancer have taken place are badly ventilated, usually with little or no sun, while they are permanently damp, not only in consequence of the materials of which they are built, but also owing to there being an insufficient fall to carry off slops or river water."

With the aid of documents and reliable observations relating to a period of more than sixty years, Dr. A. Sticker has drawn attention to a death-rate from cancer as high as at Luckau, in a village near Frankfort-on-the-Main.[1] In a single lane there were twenty-five cases, as compared with sixteen in the rest of the village. On investigation, the deaths were found to have taken place in houses standing on waterlogged ground. Was this merely fortuitous? Of course, if we draw up statistics of the occurrence in a town of any kind of accident, such as fractures of the leg, for example, it will be found that the cases are localized at certain spots. Accidents must happen somewhere, but when observations extend over sixty years, and the same streets and the same houses are always the most severely attacked, can we speak of chance then?

When statistics are closely scrutinized, it is seen that the most expressive documents are those concerning the relations of the patient to the soil; and when the indications afforded by the geography of cancer are similarly examined, the point that stands out most clearly is *the cancer house.* The idea suggested by this phrase has "caught on." Let us try to form an estimate of this danger, which, though it has been exaggerated, is no imaginary one.

In Paris, according to very old records, the same *arrondissements* are always the most severely attacked. The register kept at the Sanitary Bureau, on the proposition of Dr. Roux, will enable us to note the distribution of the cases. At present we only have the figures for the first few months, from August 1 to December 31, 1906; 1,062 cases were distributed as follows[2]: 1,008 houses with 1 death; 12 houses with 2 deaths; 5 almshouses or homes for the aged, with altogether 26 deaths; 1 house (religious community) with 4 deaths.

Almshouses and homes for the aged may be disregarded, since the conditions are exceptional, while the 1,008 isolated cases indicate nothing. Again, we need not be concerned on account of twelve houses which had two cases in six months.

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[1] A. Sticker, "Endemischer Krebs," *Zeitschrift für Krebsforschung*, Bd. v., 1906.

[2] Report presented by P. Juillerat to the Prefect of the Department of the Seine, on the work of the Sanitary Bureau in 1906.

What are these houses? A Parisian tenement house contains more inhabitants than many villages; since its population belongs to a class less comfortably off, it is subject to more rapid changes, and the history of a case of cancer may unfold itself in several successive lodgings. Merely to know the house would therefore not be sufficient; we must also be acquainted with the actual room, whether an attic or on the ground-floor. We shall not be justified in speaking of cancer houses in Paris until the Sanitary Bureau has been in operation for several decades; useful data cannot at present be furnished by large towns.

The really impressive examples are those provided by Luckau (Behla's case), and Bonames (Sticker's case), but a series of similar instances was reported a long time ago by French practitioners. The list, which is already a long one and not yet complete, is as follows:—

A house at Lyons: in 1873, a case of cancer of the stomach on the first floor; in 1875, a case in the porter's lodge; in 1877, another case on the *entresol*; in 1882, cancer of the parotid gland on the second floor; the persons attacked did not belong to the same family. A house mentioned by Shattock: in fourteen years, four cases in persons not belonging to the same family; no question of heredity, therefore. A house cited by Winter Blyth: three lodgers attacked one after the other in the same room. Three working men attacked in succession in a house in Glasgow mentioned by Scott. At Vouziers, in the same flat, the husband, wife, domestic servant, and a father-in-law died of cancer between 1870 and 1875 (Guelliot's case). At Saint-Sylvestre-Cormeilles, from 1880 to 1887, eleven cases (eight of them in the stomach), confined to a limited area, near a water-course; in 1890, a more thorough investigation of the same locality revealed a veritable "focus" in a short length of street, where there had been 21 cases (Arnaudet's case). At Oyonnax (500 houses, 4,500 inhabitants), on an average from three to four deaths from cancer every year; five in four years in three houses; from 1886 to 1890, three in the same house (the first case was that of a woman who threw some soiled rags into water which ran into a cistern; the two following cases were in neighbours). Series of cases reported by Noël (several houses);

two cases (stomach) at an interval of two years ; two cases in two years (generative organs and stomach) ; two cases in fourteen years ; two cases, both in the lip, in three years, in two adjoining rooms ; two in the same year, in a lady and her brother-in-law ; two in six months. Helen Baldwin's series of cases : five at the same farmhouse, in thirty-three years (1853, 1860, 1870, 1880, 1886) in different organs, the five patients belonging to three families ; no other case occurred in these families.[1] Alexandre Lambrior's series of cases : a house at Jassy, in the low-lying part of the town, near a stream ; family A occupied it five years, one case ; family B, four years, two cases ; family C, four years, one case ; family D, one year, one case in the following year ; families E and F lived in it for three years, one case (two years after leaving the house), followed by another ; the house remained unoccupied for eighteen months ; then came family G ; two years after its sojourn in the house, one case, plus another in a sub-tenant. In the end this fatal house was destroyed in a fire.[2] To this list should be added the houses mentioned by Aschoff, Behla, Kolb, and Sticker, referred to above.

It is always the dampness that is incriminated ; we are told that the majority of these dwellings are "mushroom-beds." How is it, then, that the installation of drainage systems at Passau, in Berlin, and in Munich does not appear to have improved the sanitary situation as regards cancer ? Experts have stated that works of this kind prevent dampness from increasing, but do not make damp houses dry. On the same piece of ground, the houses are not all equally good. We must take into account the materials of which they are built, and it may be noted that there are 45 litres of water in a cubic metre of badly seasoned wood. Kolb tells us that, in Bavaria, it is said by certain builders that a great deal of water is introduced into a building by wetting the bricks in order to make the mortar adhere to them better ; houses are hastily built, and occupied too soon.

Such is the evidence that has suggested the hypothesis of a microbe—unknown—of cancer, living in damp soils, and

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[1] A friend of ours has told us of five cases in the same house, in the country.

[2] Reported by Filassier, *Gazette Médicale de Paris*, August 15, 1907.

passing thence into damp houses. Behla dwells on ditches containing stagnant water, and on the possibility of the microbe being transferred from these in the process of watering gardens and so carried by vegetables, or of its being disseminated by certain insects. Kolb incriminates the moulds that grow on walls, or on unpaved floors, especially those of wine-cellars ; he states that, in Bavaria, waitresses (*Kellnerinnen*) are very frequently attacked. This author advises women always to wear the sanitary towels that they are accustomed to wear only periodically, in order to protect themselves from the dust raised in walking. Metchnikoff has for a very long time suspected the soil as being the origin of the disease, and food (fruit and uncooked vegetables) as the vehicle.

Cancer is certainly not contagious like smallpox or cholera ; neither is it liable to great endemic outbreaks, like plague in India, otherwise it would pass from one side of a street to another, and would spread through entire towns. If a microbe exists, it must be capable of being preserved for long periods in the soil, must awake with difficulty from its latent condition, and be transmissible to man only by a complicated process of inoculation.

That the disease is endemic has been shown by observation in the case of human beings, and confirmed experimentally in breeding mice for the study of cancer. Just as there are cancer houses, so there are cancer cages ; it is to this experimental fact that the importance of alleged instances of cancer houses is due.

Domestic measures against cancer must therefore henceforth be recognized as a branch of hygiene ; we must make up our minds to this, even though it imposes sacrifices, the necessity for which may not always be proved by the event ; all preventive hygiene makes the same demand. Drain, inspect your ditches and sewers, and ventilate subsoils. I would unhesitatingly condemn a damp house situated on wooded ground in the country, in which there had been three cases of cancer in ten years ; but we know too little about houses in towns, the history of their inhabitants, or their changes of abode, to condemn such habitations because one or even two cases of cancer have occurred in them. This is all the advice that can possibly be given to those responsible for the lives of others.

The idea that cancer is endemic has been evolved by modern hygiene ; old writers, on the other hand, believed it to be contagious. A discussion on the subject took place at the Academy of Lyons about the year 1773. Zacutus Lucitanus, in a work dated 1649—" De praxi admiranda "—tells the story of a poor woman who had cancer of the breast ; she and her three sons slept in the same room ; all three sons contracted the disease, and two of them died from it, while the third recovered (?). Nicolaus Tulpius speaks of a lady who suffered from the same malady, and states that her maid was also attacked after nursing her mistress with great devotion. Junker, a pupil of Stahl (" Conspectus chirurgiæ," 1731), believed that cancer is inoculable, though with difficulty ; his view, that it is necessary for the inoculation to be made in a suitable spot, where there is a lesion of the skin, is one that would not be rejected by a modern surgeon. At Reims, in 1750, those suffering from cancer were refused admission to the Hôtel-Dieu through fear of contagion, and Jean Jodinot, Canon of the Cathedral, set apart the sum of 25,000 livres (about £1,000) for the foundation of a hospital for cancer patients. The hospital was built in the town, but the neighbours raised an outcry, and in 1778 the cancer patients were relegated to a lazaretto situated outside the town, which had formerly been used for those suffering from plague. It was not until 1841 that the cancer patients were again received at the Hôtel-Dieu—in a special department.

If cancer be contagious, it must inevitably attack a husband and wife living together ; *double cancer* is a rough way of putting it, but the phrase is expressive. In the numerous examples that have been collected, it is sometimes difficult to distinguish between the influence of cohabitation and that of the house, and the cases are not always very reliable.

Guelliot has collected 103 cases of "contagion," eighty-four of which were between husband and wife, and the remainder between people living in the same house, employers and servants. Smith (New York) reports a case between husband and wife. Behla has personally observed fourteen such cases at Luckau : husband and wife, with an interval of three years (between the deaths) ; liver and kidney ; stomach and liver, interval of forty years ; generative organs

(wife) and kidneys, *in the same house*, interval of five years; stomach and stomach, interval of two years, *same room;* skin (wife) and organs of generation, interval of seven years; stomach and stomach, interval of eight years, *same house;* intestine and intestine, interval of eighteen years, same house; stomach and bladder, interval of twenty-one years, same house; stomach and stomach, interval of fifteen years; liver and liver; stomach and œsophagus, same house, interval of twenty-one years; stomach and stomach, interval of nineteen years, same house; œsophagus and nose (?), interval of thirteen years; stomach and intestine, interval of one year, in a very dirty house. Behla reports, on the authority of colleagues, five other cases of conjugal cancer.

Boas (Berlin), among 200 cases in the stomach and intestine, has noted twenty-two "family" cases, five of which were conjugal; in none of these instances could there be any suspicion of heredity.

Cases in which one or other of those in attendance upon a cancer patient contracted the disease.—A man, aged 55, died of cancer of the rectum in 1893; his son-in-law administered to him a nutrient enema every day for about a year and a half; this man had a cancer of the lip in the following year, and his wife developed a tumour in the breast; there was no previous case in the family (this one was reported to Behla by Dr. Elsler "upon oath"). A young woman had cancer; her mother had died of cancer of the intestine, and a (maternal) aunt of cancer of the generative organs. The young woman had nursed her mother and had made use of the same toilet instruments (Boas's case). A woman developed cancer in the finger; she washed the linen of her husband, who was suffering from cancer. A woman had cancer in the face, and the dressing was done by her son-in-law, a chemist; the latter contracted cancer of the nose (Morau's case).

Cases of more intimate transmission between corresponding organs.—Twenty-three cases collected by Guelliot, five by Hall, three by Langenbeck, one by Demarquay, one by Thomas, one by Duplouy, nine by Watson and Hays and by McEwen, one by Tross, who mentions that the anatomical structure of both tumours was precisely the same.

Transmission, in the same subject, from one part of the body to another.—Twenty-two cases reported by Ebert (lip to lip,

gum to gum, tongue to palate). Cancer has been known to develop at the spot at which a puncture had been made (Ebert, Gerhardt). A woman seen by Kaufmann had a cancer on the back of the hand and subsequently another in the corner of the eye.

It has been remarked that cutaneous cancer is not found in the parts of the body, such as the back and loins, that are not touched.

Every case should be considered and criticized; the necessary documents are not always available.

Do doctors and surgeons contract the disease? In ten years, Budd saw five surgeons attacked by cancer in the same hospital. Emson succumbed eight months after accidentally cutting himself in the course of an operation, and Alibert is said to have infected himself in the same way. The rarity of such cases is doubtless due to the scrupulous cleanliness of surgeons, and the care taken by them in rendering the hands aseptic, which may protect them from cancer as from other infectious diseases.

De Bovis does not believe that cancer is transmitted in this way by contact; were it really so, he says, such cases must be more numerous. In the course of an inquiry conducted in Belgium and extending over thirty years, Gallet and Deschamps did not note the occurrence of a single case of cancer among hospital nurses, nor did they know of one among male attendants; in Brussels, in six years and a half, there was not a single death from this disease among doctors. We may reply to this that their immunity was due to professional precautions.

A considerable number of the foregoing cases amount to instances of cancer houses; in several of them, however, there is certainly something more. The authenticated cases are too few in number to enable us to draw a definite conclusion from them. What are we to say of cases occurring at intervals of ten, fifteen, or twenty years? Even though we admit a long period of incubation, we must return to the idea of an unknown agent that continues to exist outside the individual; that is to say, we must come back to the conception of the "cancer house." [1]

[1] According to the statistics of Weinberg and Gastpar, already referred to, the death-rate from cancer among married people is to the total death-rate from the disease as 1·01 or 1·2 is to 1; the difference is insignificant.

What one theory gains, another loses ; the more confident we become that cancer is endemic or contagious, the less do we believe that it is hereditary : this is precisely what happened in the case of tuberculosis.[1]

The following cases are almost paradoxical ; the name of the surgeon by whom they were recorded is given in parentheses at the end of each series. In 1788 a woman died from cancer of the breast ; in the following generation four of her daughters died of the same disease ; then ten of her grandchildren, and lastly a woman in the fourth generation (Broca). In one family there died of cancer the mother, two daughters, and seven grand-children (Paget). A peasant, three daughters and two sons, two sons-in-law and a daughter-in-law all died of cancer ; also a day-labourer, his two sons, three nieces and two nephews (Niquet). The following died from cancer : a father and son ; a husband, wife and daughter ; two brothers and an uncle ; two brothers, an uncle and a cousin ; two brothers ; a brother and sister ; a mother and two daughters ; three sisters and a niece ; a mother and son (Behla ; almost all of these cases occurred at Luckau). It is estimated by several authors that one-tenth of all cancer cases are hereditary ; by others the proportion of hereditary cases is placed at 15, 24 and 29 per cent. Rebulet (*Revue des Maladies cancéreuses*, 1896) incriminates consanguineous marriages, in consequence of what he has observed at Bourgthéroulde : "Among the inhabitants of this locality," he writes, "there are but five or six names."

The old cases excite suspicion ; they are too extraordinary, and a doubt arises as to the reliability of the diagnoses. The facts, in so far as they have any probability, would seem to indicate contagion due to domicile. It often happens that we know nothing of the family antecedents of a patient, except what he tells us ; patients are prone to fancies, and the notion of heredity is extremely popular ; family antecedents, like family likenesses, may be purely imaginary. Facts do not

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[1] The facts collected as to goitre and cretinism—still a very mysterious problem—may serve to illustrate these notions of endemic occurrence, contagion, heredity, &c. See an admirable paper by Léon Bérard, "Goitreux et crétins," *Revue de Paris*, November 1, 1907.

permit us even to speak of heredity through the agency of the soil; if such a thing exists, we have no proof of it. At the Middlesex Hospital, in 1904, among 106,000 patients, 6,000 were suffering from cancer; the families of 3,000 of these cancer patients, and of 417 not suffering from cancer, were examined in connection with malignant disease: not only did the results of the investigation afford no evidence in favour of heredity, but they tend to show that the descendants of cancerous persons would be less likely than others to become infected. The second of these conclusions, however, is not yet definitely established.

Our opinion will be decided by experimental facts; among laboratory white mice no one has ever observed or succeeded in producing a single case of hereditary cancer, and there is every reason for believing that cancer is no more hereditary than tuberculosis.

A contagious disease is transmitted by direct or indirect contact, the intermediate agent being the air or water, as in smallpox, measles, and enteric fever; this is not the case in cancer. There are infectious diseases which cannot be called contagious because, in order that they may be transmitted, there is need of a living agent, whose business it is to carry and inoculate the germ. This agent is merely a carrier in simple cases, as, for instance, in that of plague, which is carried by fleas; it is an *intermediate host* in those cases in which the germ has to accomplish a developmental cycle outside the organism to which it will convey a disease (example—the *Anopheles* mosquito and the parasite of malarial fever).

When transmission is possible only through a development of the germ in the external medium, it is designated by an old term which has been revived, and we speak of a *miasmatic* disease. The relations between cancer and the soil, and the facts that suggest the idea of a difficult and complicated transmission, would seem to place cancer among the miasmatic diseases; the "miasma," however, is still unknown to us.

The earliest experimenters essayed to produce tumours artificially, according to the ideas current at the time. It was said that "blows" and prolonged irritation caused cancer; but it was in vain that animals of the most widely different kinds were subjected to contusions, corrosions, and friction of all

sorts, with the help of all the chemical and mechanical methods available ; in no case did the treatment lead to the formation of a cancer. According to Cohnheim, tumours arise from a group of cells which, in an adult organism, have remained in an embryonic condition, and one day begin to develop on their own account after a long period of latent life. The attempt was therefore made to graft on animals fragments of embryonic tissues possessing the energy of very young cells, but in every case they were absorbed without giving rise to a tumour. These attempts were recently repeated by Leo Loeb, a skilful experimenter, but always with a negative result.[1] Towards the middle of the nineteenth century, experiments were made in the inoculation of cancer from man to man, on several occasions with success ; similar inoculation experiments between man and animals never succeeded ; inoculation experiments between one animal and another only succeeded in the case of two animals belonging to the same species and zoological variety. It was, however, observed by Virchow that these transplantations were merely *grafts* of tissues already formed, and not inoculations similar to those performed in the case of infectious diseases.

From 1894 onwards, after the fundamental work of Morau, investigators, including among others Jensen, Borrel, Ehrlich, and Bashford, found the material for their researches in mice, rats, and dogs. It is recognized by these experimenters, however, that their results are subject to Virchow's radical criticism.

In experiments on mice, we start with a spontaneous cancer, which has been discovered on the belly of a mouse, and has originated we know not how. Two problems present themselves for solution : How were the first cancer cells produced ? And secondly, once these cells are formed, what is their destiny, and what are the conditions of their growth and vitality ?

The answer to the former problem was sought for by the earliest experimenters, who, inspired by a popular idea, endeavoured to provoke the *birth* of a cancer by "blows" ; the answer, however, has still to be found. Those who have made

[1] *Journal of the Pathological Society of Philadelphia*, April 11, 1907.

endless variations in the transplantation of cancerous tissues from animal to animal have discovered facts of the highest interest for medicine and general biology. They supplied the answer to the second question, but the real problem of cancer is comprised in the first.

Thus we have two schools, two attitudes of mind towards this problem, and two theories of cancer. Some seek to understand how the normal, disciplined, and orderly cell changes into a diseased, revolutionary, and anarchical cell, and they assume the existence of a virus which establishes itself and develops either among or within the cells ; this is the theory that holds cancer to be infectious. Others avoid this idea, and consider the cancer cell as the actual parasite, its pathogenic power being nothing else than its energy of growth. This is the cellular or anatomical theory. The especial strength of each theory lies in the weaknesses of the other, and we now await the decisive discovery that shall supply the higher point of view, where what is true in both shall be in agreement, and the deficiencies shall be supplied.

Tissues riddled with tubercle may be pounded into a pulp, in which not a single cell remains intact ; so long as the bacillus is there, as many successful inoculations may be made as desired, *in a series*, one after the other. If, simultaneously with the bacillus, entire cells be inoculated, the bacilli will survive, while the cells die and are absorbed. Here we have the type of disease that stamps its imprint on the cells, but is above all infectious and inoculable. If a similar pulp be made from cancerous tissue and the cells be destroyed or eliminated by means of pounding, heating, filtration, or desiccation, all inoculations will be unsuccessful. The *rôle* of the cell alone is apparent, and we are able to transmit cancer only by grafting entire cancer cells.

A few cancer cells, planted in an organism ready to receive them, will multiply and produce millions of cells. Suppose that we make a series of transplantations from mouse to mouse, taking, for each generation of cancer, as many mice as will enable us to graft all the cancerous tissue at our disposal : starting with a tumour of the size of a hazel-nut, in sixty generations we shall produce a mass of cancerous tissue equal to a cube, the side of which would measure a thousand milliard kilometres. . . .

The cancer cell is therefore endowed with boundless vitality and prolificness ; it is imperishable.

"Experiments have proved," writes one of the most distinguished specialists on the subject,[1] "that all the tumours successively developed in the series of positive inoculations are entirely composed of daughter cells, descendants of the cells inoculated at the outset from the first spontaneous cancer. *Everything takes place as though these cancer cells, once formed, had assumed in the animal organism the properties of vegetable cells :* thus in gardening, by means of cuttings set in suitable soil, we can reproduce indefinitely the original plant. Once the cancer cell has come into being, its power of multiplication knows no bounds. This conception of the *perennial nature of the cancer cell*, which has been acquired by experiment and is of quite recent date, removes us from all the facts already known in pathology, and is in itself sufficient to distinguish cancer from all the other virulent diseases with which we are acquainted . . . ."

But though this vitality and fecundity have no analogues in pathology, such are nevertheless to be found under normal conditions of existence. Certain resemblances have been pointed out between cancer cells and germinative cells—those upon which in an organism, whether animal or plant, devolves the task of giving birth to a new creature and perpetuating the species.

Some strange bodies that were noticed in cancer cells beside the nucleus were formerly described as cancer microbes. It has, however, been proved by minute observations that these bodies are not parasites, but are formed by a portion of the cell substance, which develops in the cancer cell in the same manner as in the germinative cells of the testicle and ovary (*cf.* Borrel, Farmer, Moore, and Walker).

In the infusoria, an individual has only to divide into two in order to produce two individuals, and so on in succession ; this is the habitual mode of multiplication in these animals. A

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[1] A. Borrel, "Le Problème du Cancer," *Bulletin de l'Institut Pasteur*, July—August, 1907. This highly original memoir, which is illustrated with extremely beautiful figures, should be read by all who are interested in the question of cancer.

moment, however, arrives when the divisions cease to take place, as though the "race" were fatigued or exhausted. Two infusorians then approach one another, adhere together, and exchange a portion of their substance; this *conjugation* rejuvenates them, and the series of successive divisions commences afresh, and continues until a new conjugation becomes necessary; this is the *caryogamic rejuvenation*, so well known since the works of Maupas. Now, in malignant tumours conjugations of cells have been described, to which has been attributed the same value as to the conjugations of infusoria (Farmer). The cells in conjugation were sometimes two cancer cells, sometimes a cancer cell and a leucocyte.

It has recently been suggested by Hallion,[1] that the proliferative energy of cancer cells might be explained by these processes of rejuvenation or fecundation, and in the absence of proof we can at least recognize the ingenuity of the author in question. The conjugation between leucocytes and cancer cells is not, however, absolutely proved; it is, perhaps, rather an act of *phagocytosis* on the part of cells, which, instead of uniting, are devouring each other.

At a given moment, a living cell divides into two, by a process termed by scientists *mitosis*, in which we can follow, through different phases, the movements and distribution of minute particles of nuclear substance, which are known as *chromosomes*. Each cell in the body of a given animal contains at this moment a fixed and constant number of chromosomes, say twenty-four. In the germinative cells of the same animal, towards the end of their development, the number of chromosomes is only one-third of that in the ordinary cells; we say, in technical language, that the binary division of the germinative cells is a *reduced mitosis*. Now in cancer, in the zones of growth and invasion, the cancer cells divide like germinative cells by reduced mitosis (*cf.* Farmer, Moore, and Walker).

The occurrence of reduced mitoses in the cells of malignant tumours has, however, been disputed by observers, who had begun by believing in them (Bashford and Murray). Even though they exist, they must have a cause which has yet to be found; they are not an explanation in themselves.

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[1] *Journal de Physiologie et de Pathologie générales*, March, 1907.

All these analogies are distant ones ; we must not descant too much on the theme that cancer cells are the only ones in nature that possess an immortality comparable to that of germinative cells.

By Ehrlich, who is one of the upholders of the anatomical theory, no such exalted properties are attributed to the cancer cell. In the opinion of this authority, its energy is entirely relative, and, instead of an over-excitement of the cells in the tumour, there is decadence on the part of those composing the rest of the organism. Cancer, he holds, develops only in an individual in a depressed and enfeebled condition ; hence its frequency at the commencement of old age, the transformation of benign into malignant tumours, and the *rôle* attributed to heredity. This is still the cell theory, merely pitched an octave lower. It remains to its partisans to crush their opponents with questions that receive no answer. "Why," say they, "is no inoculation successful unless the matter inoculated contains intact cells? Show us this cancer virus that you speak of!" And it must be admitted that they have a fairly strong case.

Not only have thousands of mice been bred for inoculation purposes, but the litters have been kept under observation, in order to detect the initial cause of the spontaneous tumours that are subsequently capable of being transplanted indefinitely. The cages, food and methods of crossing have been varied, under conditions easier to recognize than those governing associations of human beings, and observations have been collected which have the value of experiments.

Mouse cancer[1] is endemic like human cancer, and there are cancer strains and cancer cages. The first indisputable instance was found by Borrel, and was provided by an old woman, who lived in the rue Saint-Martin, in Paris, and bred mice in her room ; she had two cages, through which about 200 female mice had passed, and in two years there were some twenty cases of cancer. In a single year at the Sorbonne M. Giard observed seven cases of cancer in forty mice. At the Lignières Laboratory, at Buenos Ayres, there were eight cases in three months in the same cage.

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[1] The commonest form of cancer in mice is cancer of the mamma, analogous to cancer of the breast in women.

In the outskirts of Paris an old fellow, who is a recluse and lives in a very small cottage, breeds mice, which he brings to the Pasteur Institute for sale. At his establishment there were in four years more than forty cases of spontaneous cancer, and on one occasion he brought in four mice in which cancer had appeared almost simultaneously. One day a chapter of accidents led to the destruction of the whole of the mice, and the breeder was furnished with forty fresh mice, from a stock which was free from cancer. The old cages remained, however, and three fresh cases have already made their appearance. Certain breeding-places have provided Paris with as many as 10 per cent. of spontaneous cases of cancer among old female mice.

Dr. Gaylord, of Buffalo Laboratory, U.S.A., had in his possession two cages in which cancerous rats had been kept. After the departure of the rats, the cages remained empty for a year without being disinfected; some new rats, which were put into the cages in the following year, developed three tumours. In America, a breeder who kept a hundred adult female mice, producing on an average from 1,000 to 2,000 young ones every year, observed, in one of his cages, two tumours in one year. After moving, and taking the cage with him, there were forty tumours in one year. The breeder moved again, once more taking the cage just as it was, but, being annoyed at what had happened, obtained a fresh stock of mice, purchasing ten females and two males; in the following winter there were four tumours, and from twenty-five to thirty in the course of the year. In all there were sixty tumours in the one cage.

There are some important breeding establishments which are free from cancer. In that of Madame Judic (*les Nids*, near Avallon), who supplies mice to the Pasteur Institute, only a single spontaneous cancer has been observed up to the present. Dr. Bashford, of London, through whose hands at least 50,000 mice have passed, estimates the ratio of occurrence of spontaneous cancer among English white mice at 0·03 per cent. (one case of cancer in 3,500 mice).

These multiple cases cannot be regarded as due to heredity, since the cages continue to be dangerous in spite of the stocks of mice being changed; it is as though there were some

local cause of contagion in the cages themselves. Experiments are being made to determine the influence of external conditions, such as humidity, and of conditions such as nutrition, which may be termed internal. "Very delicate modifications in the organism of the mouse, perhaps due to the diet, whether liquid or solid, may have a great effect on the fate of the cancerous graft. These facts are not without parallels in science. It has been shown by Rosenau's experiments that guinea-pigs fed upon horseflesh were *rendered susceptible* to inoculation with horse serum. From a verbal statement by Dr. Zalensky, it would appear that the Tartar peoples, whose food mainly consists of horse flesh, exhibit to an excessive degree the complications due to injections of antidiphtheritic serum, which is derived from the horse."[1] Pellagra, a disease which is still highly mysterious, is attributed to the use of maize for food; from the recent investigations by Tizzoni and Panichi, pellagra would appear to be caused by a microbe, which, however, produces the disease only in organisms fed upon maize. In infectious diseases the microbe is not everything.

The fact that cancer is unlike other diseases, and that the virus is unknown, is not a reason for denying the existence of the latter. Ignorance is not a proof, and we must continue our researches. It is scarcely fifty years since the study of infectious diseases was first begun, and that of diseases due to foods has hardly commenced. We do not know all the secrets of Nature!

A fact of primary importance, that no one denies, is that the cancer cell behaves like a parasite; but it is possible that it is infectious because it is infected. The mind cannot rest satisfied with the idea of a cell diseased we know not how, for no reason, and as it were by a freak; it seizes upon the notion of *symbiosis* between cell and parasite, which has already been extensively studied in the case of several diseases of animals and plants (tuberculosis, rust in wheat, club-foot in cabbages, &c.), and the problem that it sets itself is the experimental reproduction of cellulo-cancerous symbiosis.

There can be no doubt that, in disease, the cell contributes

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[1] A. Borrel, *Le problème du cancer*.

its share; there must be cells which are ready to receive the cancer virus, and others which are not. Vaccinal virus takes *on*, but not *beneath* the skin. According to Metchnikoff's experiments, the spirillum of syphilis, if inoculated into the subcutaneous tissue, does not give rise to the disease. There are microscopic and pathogenic fungi, which do not cause disease when inoculated experimentally beneath the skin of an animal's flank, but do so when inoculated in the sole of the foot.[1] How many discoveries are due to an artifice or special dexterity on the part of the investigator! Virus conveys disease if introduced in the proper place, and we shall be able to inoculate cancer if we treat the right cell in the necessary way. Observation and experiment have thus suggested the concept of the *recipient cell.*

It may be that recipient cells exist in the normal organism; or possibly normal cells become recipient cells only after having undergone changes, either an increase in or a decay of vitality. Thus infection would take place in two stages, of which the first would prepare the soil, while in the second the virus would be introduced. The old experimenters instinctively sought to produce the first stage, when they scratched, abraded, burned and pinched the tissues in order to bring about the formation of a tumour. It is a popular idea that cancer of the breast is always preceded by a "blow," the effect of which would be to cause lesions in cells, and to render them receptive, that is to say, susceptible. The short clay pipe is accused of producing susceptible cells on the lip of the smoker; the skin exhibits small excrescences, or ordinary "pimples," which soon give rise to tumours (curable by operation), the primary lesion having resulted in the formation of receptive cells. Our epidermis is composed of several layers of cells, and those of the innermost layer are always in process of multiplication, to replace the cells that are exfoliated at the surface; these deep-lying cells exhibit a high degree of activity and energy, and, as shown by reliable microscopical observations, are frequently the starting point of tumours. The crucial experiment would therefore consist in the production of a tumour by inoculating

[1] E. Pinoy, "Mycétome expérimental," *Comptes Rendus de l'Académie des Sciences*, 1907.

a previously prepared mucous membrane with cancer juice, free from intact cells.

The small parasites of man and animals are perhaps capable of doing what we cannot. We know that fleas, bugs, mosquitoes, and flies are the living inoculators of various infectious diseases. It was reasonable to suspect that parasites may play a part in the natural inoculation of cancer, and curious observations on this subject have been made by Borrel. Cancerous mice, having tumours sometimes one-fourth of their own weight, are hampered in their movements ; they are no longer able to catch the fleas that swarm in their fur, and they are not capable of ridding each other of these parasites with the altruism of monkeys. More to be suspected even than fleas are the acari, which can burrow beneath the surface of the skin and reach the gland-ducts. In the case of rats we are acquainted with contagious "skin diseases," due to the penetration of acari, which excavate tunnels in the cutaneous tissue. In certain cases of cancer of the skin in the human subject, and in tumours of dogs, parasitic larvæ have been found in the midst of the diseased tissue ; these creatures may act in two different ways, by irritating the cells and conveying to them some virus from the soil or domicile.

Similar suspicions have been entertained with regard to internal parasites. Almost all cancerous mice in laboratories contain numerous intestinal worms ; in the case of rats there have recently been described six tumours differing in structure, in the centre of which was found the cysticercus of a tapeworm. The most curious point in this connection was that one of these tumours was successfully transmitted several times from one rat to another. Certain worms are capable of migrating from the intestine, and, by perforating the tissues, making their way into other organs ; here they wander about, carrying with them some of the microbes that are found in the intestine in countless myriads. When seeking the origin of cancer we are bound to take into consideration diet, the alimentary canal, and the intestinal flora (Metchnikoff).

Science cannot say more than this on the subject, since its knowledge extends no further. If, however, the *rôle* of theories is to suggest experiments, the microbic theory of cancer is worth more than the anatomical theory. When confronted

with the cell, heredity, and diathesis we are almost deprived of our weapons. The parasitic theory is, as Borrel says, more alluring; it impels us to continue our investigations, than which nothing can be better.

No specific treatment of cancer as yet exists, though every year empiricism makes a certain number of attempts which pass into oblivion. We hear discussions about physiological topics or cures, in which we should do well not to believe until experts have reported thereon. We have had injections of quinine and of trypsin, and in this connection it must be said that a distinction should be made between methods of treatment offering alleviation and those that promise a cure. Not long ago the discoverer of a remedy, having exhibited to a certain medical society a patient of his, after being "cured" by him, the president of the meeting, not wishing to doubt without having seen for himself, made a careful examination of the patient, shook his head, and returned to his place without saying a word. Nothing still avails us like the knife, but two methods of treatment, which have been strongly recommended with a view to assisting rather than superseding it, have already yielded something more than hope.

In the laboratory, experiments in anticellular vaccination and serum-therapy have been made on mice, the cell being regarded as the agent or virus-carrier of cancer. This is an application of the laws of immunity. We know that a living organism is a well-governed world, capable of defending itself against invasions. Whenever an inoculation is made of foreign bodies, such as microbes, blood corpuscles, cells from divers organs, poisons and toxins, the organism absorbs the injected elements by phagocytosis, and devotes itself to and accomplishes this task with increasing energy and rapidity; the blood serum frequently acquires preventive or curative properties as opposed to the hostile microbe or toxin, as in the case of horses immunized against diphtheria and tetanus. The serum of an animal that has received injections of blood from an individual of another species becomes capable of dissolving blood corpuscles belonging to this species. The serum of an animal which receives and absorbs cells from the liver, kidney, and brain acquires properties noxious to cells of this kind. It was, therefore, worth while to discover whether the serum

of an animal which had destroyed cancer cells by phagocytosis, and digested them, would be capable of exercising an effect upon an individual attacked by cancer, and serums have been prepared in conformity with this principle. It is not yet possible to pronounce an opinion as to their efficacy ; the trials are not far enough advanced, and we already know that even normal serums affect cancer patients in a manner which is often favourable, though very transient (Tuffier's cases). Researches of this kind upon anticellular serum-therapy are being carried out in laboratories.

According to several experimenters, a mouse that has received by injection a certain quantity of cancerous matter without developing cancer has acquired immunity ; and a cancerous mouse from which the tumour, whether spontaneous or experimental, has been removed by operation is refractory to all fresh transplantations. It has been shown by Ehrlich's experiments that a mouse, which does not become cancerous after inoculation with cancer of small virulency, acquires a very great power of resistance to a graft of highly virulent cancer. These facts have led to attempts at anti-cancerous vaccination, but this cannot yet be applied to man.

The truth is that, in laboratory experiments, it is usually a case of mice being rendered more or less resistant—we can hardly say refractory—to a *graft* of cancerous tissue ; but no conclusions can be drawn from this as to cancer contracted under natural conditions, and Bashford declares that he has observed the spontaneous appearance of cancer in mice which had shown themselves refractory to grafts. Anti-cancerous vaccination is, moreover, subject to the same limitations as are grafts themselves ; the latter prove thoroughly successful only when the mice employed belong to the same variety, and it is hardly possible to transplant a cancer from a white to a grey mouse ; a tumour which grows readily in Parisian mice is more difficult to communicate to mice belonging to Berlin. Thus, Michaelis failed to vaccinate white mice by treating them with cancer from grey mice, nor was he able to vaccinate Berlin mice with cancer from Copenhagen mice. In short, the experiments of Borrel and Bridré, Schöne and Bashford tend to show that it is less a question of *anti-cancerous* than, if we may use the expression, of *anti-mouse* vaccination, in the sense

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that we obtain approximately the same degree of resistance in a mouse when, instead of treating it with tissue from mouse-cancer, we treat it with any other mouse-tissue *whatever*, such as liver, blood, or spleen.[1] This is not a specific vaccination comparable to the methods of treatment that have already enabled us to cope with infectious diseases.

The principle of treatment by X-rays is as follows. Cancer cells are more sensitive to the action of the rays than are healthy cells; we can therefore destroy the former without injuring the latter,[2] which is often a difficult problem in practice. From experiments upon cancerous mice and microscopical examination, it would appear that the rays act by producing an inflammation, which dilates the blood-vessels, induces a flow of blood to the part, calls up reserves of phagocytes, and paves the way for the phagocytic absorption of the diseased cells. Direct action upon the cells themselves is open to some doubt.

The rays act only on the exposed surface, they have no effect upon deep-seated structures; they can therefore only cure cancers which are superficial and of small size, of the type termed by medical men *cancroid* of the skin. They certainly cure these, but no competent observer will admit that they have the power of curing, unaided, a deep-seated tumour, such as cancer of the liver or stomach, or even cancer of the breast.

The proposal to utilize the superficial action of the rays as an adjuvant to surgical treatment is a good one, since it sometimes happens that cancer, after removal by operation, reappears in the cicatrix, and to expose the latter to the rays with a view to preventing local recurrence is therefore de-

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[1] Experiments by Schöne, Bashford, and Borrel and Bridré. *See* Bridré, "Recherches sur le cancer expérimental des souris," *Annales de l'Institut Pasteur*, October, 1907.

[2] "It has been shown that the radiations are capable of killing the cells of a neoplasm, while leaving intact the tissues adjacent to or even incorporated in the tumour, and indeed experiments *in anima vili* have proved that the rays exert a similar selective action in the case of healthy tissues. Thus, in our experiments on the testicle of the rat, we have succeeded in destroying the sperm cells, while the interstitial gland and the Sertolian syncitium remained uninjured" (Bergonié and Tribondeau, *Comptes Rendus de l'Académie des Sciences*, December 10, 1906).

cidedly beneficial. Operators have indeed gone further and, after the bistoury has laid open the tissues and excised the diseased parts, before closing the wound they have brought the rays to bear upon the exposed surfaces, using, as it were as a disinfectant, a physical agent the efficacy of which is beyond doubt. To appreciate the successes obtained with the rays, it would be necessary to review and discuss the thousands of cases that have been collected. It appears certain that the treatment has already greatly alleviated suffering, prolonged life, and in a few favourable cases resulted in definite cures.[1]

In default of the rational treatment for a disease, we must have recourse to prophylactic, individual, and social hygiene. This does not work miracles, and the results are not perceptible from day to day. Hygiene, however, like education and habits, possesses the power of transforming human life.

As to hygiene of the dwelling, do not build in the water; build rather on the sand—which is permeable. Choose materials which do not retain the damp, and, in the country, endeavour to obtain a divorce between the manure heap and the house. In Switzerland may be seen charming châlets, with flower-decked balconies, having as a ground-floor a piggery, a foul hole reeking with dung and liquid filth. There are plenty of old sayings which perpetuate the dogma of the salubrity of the dunghill, and such dogmas as these might perhaps be treated with at least as much scepticism as is commonly meted out to science.

The hygiene of diet is taught by Metchnikoff. Beware of foods which import parasites into the intestine, such as fruits and vegetables (eaten raw) which ripen in contact with the soil, the reservoir of all the microbes known and unknown. By doing so you will at the same time guard against appendicitis; every endeavour should therefore be made to popularize the consumption of cooked herbs and vegetables.[2]

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[1] The application of "sparks of high frequency and high tension (fulguration)" has recently been proposed by Keating-Hart. Further study on the subject is necessary.

[2] "Microbes are conveyed into the alimentary canal above all by uncooked food, so that, in order to diminish the number of species of microbes belonging

How is it that two-thirds of the cases of cancer occur in the alimentary canal?

It is impossible to disguise from ourselves that, in France, we are living on the margin of a current which is continually passing from the intestine to the kitchen, and from the kitchen to the intestine; I refer to the spreading of night-soil over the ground. Whether it be a case of the wholesale distribution of the sewage of a large town, or of the minor operation, which consists in irrigating the kitchen-garden with dirty water and other matters highly beneficial to the soil, we buy in the market vegetables which, in spite of their fresh appearance, are polluted with all the microbes of the human intestine. There are medical reasons for preferring to sewage distribution the forced purification in confined spaces known as biological purification, which has recently been so well studied by Calmette and his collaborators.[1] In the meanwhile, cook your vegetables, and sever the unfortunate connection between food and the dunghill.[2] This is the essential prescription in anti-cancerous prophylaxis.

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to the intestinal flora, it is advisable to eat only cooked foods and to drink only what has been previously boiled. Under these conditions, although the whole of the microbes in our food and drink are not destroyed, since certain of them resist a temperature of 100° C. (212° F.), the vast majority are certainly killed" (Metchnikoff, *Essais optimistes*, p. 211).

1 "*Recherches sur l'épuration biologique et chimique des eaux d'égout*," 1905-07.

2 Anti-cancerous hygiene will apply more particularly to rural districts. If certain information is to be trusted, a serious attempt is now being made to improve country sanitation; there is at the present time so much daily intercourse between the country and the towns, that a continuance of the former state of apathy as regards such matters is no longer possible, and we can but commend the circular letters recently addressed by the French Minister of the Interior to the prefects, with a view to the application of the law of 1902. The documents in question appeal to the local authorities to "instruct the nation in matters of hygiene." Within the last eighteen months it was announced that the municipality of Bourg was preparing to hold an exhibition of rural hygiene in 1908.

THE PROBLEM OF TUBERCULOSIS.

I.

The treatment of tuberculosis is the most urgent of the problems with which experimental medicine has to deal. At the Congress held at Paris in October, 1905, at which Professor von Behring announced a definitive method of cure, the words of the illustrious scientist naturally excited the keenest attention. The importance of the announcement will be duly appreciated, when we recall the efforts that have been made with the same object during a period of more than twenty years. How is it, the reader may ask, that tuberculosis has not been cured by the methods that have been successful in the case of small-pox, anthrax, plague, tetanus and diphtheria?

For infectious diseases, science has so far introduced two methods of treatment, which stand as the classic types of the new therapeutics—vaccination and serum-therapy, and it was logical that these should be applied to tuberculosis. I desire to show why they have so long proved useless; their failure is to be explained by the nature of the infection, the properties of the bacillus, and the special difficulties of making experiments. The story of tuberculosis is a commentary on the precept in which, in the face of unforeseen difficulties, the tenacity of the genius of Pasteur expressed itself: "Let us perform the same experiments over again; the essential point is to persevere."

When an organism is vaccinated against a disease it is artificially infected with a benign malady, which does not kill it, but confers upon it the power of resisting a serious attack. Vaccine is a weak virus, which gives immunity. There are two kinds of vaccination, in one of which the weak virus is provided by Nature, while in the other it is manufactured by man. In Jenner's vaccination, in order to render man immune to small-pox, he is inoculated with the vaccinal virus, which is,

in all probability, nothing but an attenuated small-pox virus derived from the cow. In Pasteur's vaccinations, the vaccine is a virus artificially weakened by laboratory methods. In the hands of Pasteur, the virus of anthrax became vaccine by culture at an abnormal temperature, while the virus of chicken-cholera underwent a similar modification through growing old in the stove in contact with the air. Against certain human and animal infections, Pasteur's principle of attenuating virulence by vaccinating with microbes that have been killed has been pushed to an extreme, and the method has been attempted for the prevention of cholera and plague. In short, in order that vaccination against a disease may be possible, the primary condition is that the microbe of this disease should have experienced in a natural state different adaptations through parasitism in different species (small-pox and vaccine); or else that it lend itself, by laboratory methods, to variations in virulence.

We are not yet capable of making a chemical analysis of the modifications produced by the benign malady in the vaccinated subject; but the biological conditions of immunity have been revealed to us by the talented researches of Metchnikoff. What with facts and theories, "phagocytosis" has become a popular doctrine. The most modest manual explains how the white blood corpuscles, or *leucocytes*, ingest and digest the microbes that they have seized; for phagocytosis is the simplest and most general form of digestion in living beings. Thus, for a microbe to be able to become a vaccine, the second condition is that it be absorbed by the leucocytes of the inoculated animal.

Leucocytes are cells that protect an organism; they are motile, and ubiquitous, and interpose between the cause of a disease—whether microbe or toxin—and the cells that are susceptible to these agents. It is, however, difficult to understand how it would be possible for immunity to be established in the case of a disease which attacks the defensive cells.

In the serum-therapy of von Behring and Roux there are two stages, a preliminary immunization of an animal against a certain malady, and the subsequent injection of the serum of this animal into another suffering from the disease. Within the body of the former animal is evolved a remedy which

we are unable to produce artificially, and it is this that we administer to the patient. The use of the serums for tetanus and diphtheria have tended to popularize this treatment.

It is above all the toxic diseases that are curable by serum-therapy, caused as they are by a microbe which is not generally distributed through the organism, but takes up its quarters at a certain point in the skin or in a mucous membrane, and there secretes a toxin which spreads through the organs and attacks the cells that are sensitive to it, just as, for instance, the nerve cells are attacked in the case of tetanus. These toxins, which are extraordinarily violent, exhibit in a large measure the same reactions as the bodies termed by biological chemistry ferments or diastases. They can be attenuated in the same way as microbes are attenuated ; they can be inoculated, in infinitesimal doses, into a powerful animal such as the ox or the horse ; the animal becomes accustomed to them, and its blood acquires fresh properties, for, when mixed in a glass tube with several lethal doses of the toxin, it neutralizes them, and when introduced into the body of an animal susceptible to the disease it preserves or cures it. In the immunized animal, to combat the poison, the phagocytes have secreted a counter-poison, or anti-body, which is a natural remedy capable of being conveyed from one organism to another.

There are vegetable poisons, such as ricin and abrin, and animal poisons, such as snake venoms, which behave like the microbic poisons of diphtheria and tetanus, and to counteract which serums can be obtained. There are also vegetable poisons, however, which do not possess the same properties, such as, for instance, those that are extracted from the Solanaceæ and Strychnaceæ. It is very possible that there are microbic poisons, which likewise do not lend themselves to the production of antitoxic serums ; and unhappily, so far as our present knowledge goes, the poison of tubercle appears to belong to this class.

Since the discovery and the culture of the tubercle bacillus by Robert Koch in 1882, every method of treatment known in therapeutics has been tried against human tuberculosis with negative results. The data acquired in the course of experimental work, which was truly enormous, have revealed even greater differences between tuberculosis and those infectious

diseases that are conquerable by Jenner's or Pasteur's systems of vaccination and by serum-therapy.

Tuberculosis is a disease which develops in closed foci ; the bacillus does not multiply in the blood and lymph, as do the bacilli of anthrax and plague. On being arrested at some point or other in the organism, it occasions a mobilization of the phagocytes, which besiege it, wall it in, and form a nodule or tubercle in which it vegetates as a prisoner. It poisons and kills them, but the leucocytes that succumb at the centre are replaced by fresh ones at the periphery, and the tubercle increases in size and becomes hollow ; the microbes are still encapsuled within a shell, and they even vegetate in the interior of the cells. The tubercle is a tiny pathological world, closed to the normal world surrounding it. This explains how it is that the organism resists, and the disease runs a chronic course. But if, between the tubercle and the tissues, there are barriers which prevent the microbe from emigrating and becoming generally distributed, such barriers also intervene between the tissues and the tubercle, and obstruct the action of the medicaments that may be introduced into the body of the patient. The bacillus kills with difficulty, but is itself difficult to kill.

A chronic disease is one in which there is no spontaneous vaccination. Acute infectious diseases once they are conquered do not recur, and an infectious disease is chronic only because the organism is incapable of spontaneous cure by crisis. The sheep attacked by anthrax dies, or remains vaccinated ; man attacked by tuberculosis, if left to his own resources, gets on with his enemy as well as he can—he neither dies nor recovers.

There is no instance of a tuberculous animal becoming, after being cured, refractory to tuberculosis. We may recover from tuberculosis, but this recovery is not comparable to recovery from anthrax. A sheep which has recovered from anthrax has become refractory to the disease, but we are in no way entitled to assert that a man cured of tuberculosis cannot become tuberculous again. On the contrary, we are taught by observation and experiment that, ill or on the road to recovery, the patient becomes more and more susceptible to the disease. In the same way we may be cured of some passion, while remaining more susceptible to it ; besides diseases of which an attack confers immunity, there are others, an attack of which renders the patient susceptible.

The dominant fact in the natural history of tuberculosis is that the organism is smitten at the outset in its means of defence. In tetanus the specific poison makes an elective attack upon the nerve cells, but the leucocytes may neutralize it before the latter have become affected; the leucocytes, which are less susceptible cells, protect those that are more susceptible. In tuberculosis, on the other hand, there are no refractory cells, and consequently none that are sufficiently protective. The different cells are sensitive in different degrees, but all are sensitive. Against the infectious diseases in which recovery or vaccination occurs, therapeutic methods are directly or indirectly based upon phagocytic defence. But what is to become of such methods of treatment against a disease in which the phagocytes are too sensitive? What would be the state of public order in a community in which the policemen became thieves? If, instead of acquiring immunity, the organism becomes susceptible, it is because the leucocytes are destroyed, or excessively debilitated by the tubercle bacillus.

The tubercle bacillus produces a toxin, known under the name of tuberculin, which was discovered in 1890 by Robert Koch. Having injected a fresh dose of bacilli beneath the skin of a guinea-pig already suffering from tubercle, Koch noticed that the new injection, instead of, like the first, causing a persistent ulcer, merely produced an abscess which soon healed. Guinea-pigs treated in this way appeared to resist tuberculosis better than the controls, and in the case of the tuberculous guinea-pig the tubercle bacillus seemed to become a therapeutic agent. Since the injected bacilli are absorbed with difficulty, Koch conceived the idea of injecting only the favourable principle contained in them; from cultures of tubercle bacilli he succeeded in extracting the liquid, *i.e.*, soluble tuberculin. This is an extract of tubercle bacilli, which is prepared by macerating the bacilli while hot in the glycerinated broths in which they have grown. But the actual bodies of the bacilli, after being killed and desiccated, still constitute the best tuberculin.

The substance of the tubercle bacillus as a medicament for tuberculous infection: from this paradoxical fact we have, under the name of "Koch's lymph," the first systematic remedy for tuberculosis. On consulting the medical journals for the

years 1890 and 1891, the reader will find on every page, following communications from Koch, categorical and enthusiastic statements in confirmation, dithyrambic eulogies, and pæans of thanksgiving to the "saviour of humanity." It is like a procession of scientists coming to inscribe their names at a festival to celebrate the supreme conquest by scientific medicine. Then "the tumult and the shouting dies," and to the enthusiasm succeeds a disfavour, unjustified as regards a discovery of immense biological import.

From the very beginning Koch saw that tuberculin takes effect, not upon the tubercle bacillus, but upon the tuberculous tissue. "The remedy destroys, not the tubercle bacillus, but the tuberculous tissue." Within the cavity of the matrix-like mass formed by the cells on which it is parasitic, and which it injures and kills, the bacillus is not altogether at its ease, since the situation becomes highly unfavourable to it. Tuberculin hastens the decay and death of the bacillus by exercising a similar effect upon the cells surrounding it; it kills it by acting in the same way as the bacillus itself. The important point was to discover to what lengths this treatment might be carried. Neither of the known general methods of procedure, whether vaccination or serum-therapy, is superseded by this paradoxical remedy.

Papers without number have been published upon tuberculin, which is a poison having no resemblance to the toxins of tetanus and diphtheria, which are neutralizable by antitoxins. It cannot be compared to the ferments or diastases; it resists a temperature of 250° C. (482° F.), while the diphtheritic toxin is destroyed in twenty minutes at 100° C. (212° F.). When a healthy guinea-pig is inoculated with tetanic toxin (without any tetanus microbes), the animal is killed with all the symptoms of tetanus; but if a healthy guinea-pig be inoculated with even a considerable dose of tuberculin nothing resembling tuberculosis is produced. A very weak dose (20 milligrammes) of tuberculin, however, inoculated subcutaneously, kills a *tuberculous* guinea-pig in a few hours; if inoculated in the brain, a dose of one-thousandth of a milligramme is fatal. This is a new and original fact in science; here we have a microbic toxin noxious only to the organism already infected by the microbe that produces it; a toxin that, in a minimal dose, in Koch's first

therapeutic experiments appeared to act upon the sick animal like a remedy, and that, in a stronger dose, acts as a deadly poison.

In a general way the effect of tuberculin upon man is similar to its effect upon the guinea-pig ; taking into consideration the difference in weight, however, a tuberculous man is about 3,000 times more sensitive to tuberculin than is a tuberculous guinea-pig. A tenth or a twentieth of a milligramme occasions a violent outburst of fever, with prostration and general depression. This febrile reaction, which, however minute are the active tuberculous foci, is produced in a tuberculous subject by the inoculation of a weak dose of tuberculin, is employed as a means of diagnosing the disease. This mode of examination is somewhat rarely practised in the case of human beings, whose susceptibility is such as to entail extreme caution ; but it is commonly employed in the case of animals, especially cattle. Tuberculin, by facilitating the work of sanitary inspectors, has rendered signal service in the prophylaxis of tuberculosis.

Tuberculin does not exhibit the properties of the toxins of diphtheria or tetanus, upon which serum-therapy is based ; it it has not yet been observed to produce in the inoculated organism the counter-poison, or antitoxin, which can be conveyed to another organism. Neither the serum of an animal into which tuberculin has been injected nor that of one suffering from tuberculosis can be made use of as a therapeutic agent. Nevertheless there are anti-tuberculous *serums*, and unfortunately there are several of them, while there is but one for diphtheria, *the* anti-diphtheritic serum ; there is no indication here of definitive therapeutics.

The anti-tuberculous serums that have attracted most attention are those of Drs. Maragliano and Marmorek. The impression left on the mind of the reader after perusing communications from Maragliano is that, in a problem bristling with difficulties, the author has met with none. It would appear that in his hands, as regards tuberculosis, the typical experiments that resulted in the serum-therapy of von Behring and Roux were uniformly successful. The results on tuberculosis in the first and even in the second stage, for no one boasts of curing phthisis, would seem to have been more than

encouraging, and actually decisive. We find ourselves confronted with one of the contradictions that are of such frequent occurrence in this subject ; on the one hand we have the optimism of the discoverer, and a certain number of favourable results reported by honourable and impartial physicians ; on the other, a remedy which scarcely becomes known, and in many cases falls into oblivion. The fact is that the remedy is not a cure, or is not so for long.

More original is the attempt by Dr. Marmorek, who is said to have found a new vegetative form of the tubercle bacillus, and a new toxin distinct from the tuberculin of Koch. It would appear that Koch's tuberculin is not the true tuberculous toxin, but a substance which, when injected into a tuberculous organism, causes the true toxin to be produced by the bacilli. The true toxin would, it is said, provide an efficacious serum, and experiments upon man have yielded a certain proportion of favourable results. It must, however, be added that the experiments upon animals, performed by experienced scientists who desired to test the system, have not proved convincing.[1]

In the present state of science, there is no anti-tuberculous serum and no serum-therapy for tuberculosis. How, then, are we to explain the optimism of honest investigators, and the favourable results reported by clinical physicians, whose competence and impartiality are beyond doubt ?

Experiments upon guinea-pigs are not identical with those upon man ; the results are not the same in the case of a small animal of 400 to 800 grammes ($\frac{4}{5}$ to $1\frac{3}{5}$ lb.) and in that of a man weighing from 50 to 75 kilogrammes (110 to 165 lb.). In infectious disease, the host is a factor of no less importance than the microbe. In the second place, the results obtained with various anti-tuberculous serums resemble very closely those yielded by tuberculin in minimal doses. These serums

[1] It is right to mention the testimony in favour of Marmorek's serum, given by Levin, of Stockholm, and Hoffa and Hüllen, both of Berlin. The encouraging results were always observed in cases of osseous or glandular tuberculosis ; no amelioration was apparent in cases of tuberculous arthritis, and no mention is made of any success having been achieved in pulmonary tuberculosis. Hoffa's conclusion is that the action of this serum must be attentively studied, but that we are still far from being able to form a definitive appreciation of its therapeutic value.

must act through the traces of tuberculin contained in them, and in certain forms of tuberculosis tuberculin has a favourable effect. The clinicians of fifteen years ago, who were so enthusiastic over Koch's lymph, did not discover the facts. Cases are on record in which cutaneous and osseous tuberculosis have been cured by tuberculin, and the favourable results from Marmorek's serum appear also to have been obtained in the same forms of the disease, which are known as surgical tuberculosis. The anti-tuberculous serums are very probably nothing but Koch's tuberculin in disguise.

Tuberculin, administered in minimal and progressive doses, with the precautions enjoined by Robert Koch and perfected by his pupils, finally no longer produces in the tuberculous subject the specific febrile reaction. This fact has been regarded as a proof that there is such a thing as immunity to tuberculosis ; it is, however, necessary to understand what we mean by this phrase. If we employ the term immunity in the sense in which it is used in the case of diphtheria or tetanus, we cannot speak of immunity to tuberculin. It is only a case of becoming used to it, analogous to what can be obtained with alkaloids, while an organism immunized to the diphtheritic toxin is rendered immune to the bacilli of diphtheria. Now, the supposed immunity to tuberculin in no way involves immunity to the bacillus of tuberculosis. In a patient who no longer reacts to tuberculin, tuberculosis may continue to progress, and it has long been known that very advanced cases of tuberculosis cease to react to tuberculin. Thus, in tuberculosis, the two orders of phenomena, infectious and toxic, do not appear to be as regards each other in the relations of dependence such as are known in diseases like anthrax or diphtheria. The failure up to the present time of anti-tuberculous serum-therapy is but too readily explicable.

The tubercle bacillus does not lend itself to the absorption by phagocytosis, which is the essential condition of vaccination. It is impregnated and enveloped with a fatty, waxy substance, which protects it in the external medium against the agents of destruction—hence its great power of resistance in dry dust—and, in the organism, against the action of the phagocytes. Dried bacilli contain more than 40 per cent. of fatty substances, neutral fats, free fatty acids, lecithin, cholesterin, &c. When

extracted by means of ether and chloroform and injected subcutaneously into a guinea-pig, these inert and dead substances, which are difficult to absorb, produce an abscess and are discharged with the pus, just like dead bacilli. It is in truth to these substances that are due the difficulty of absorption, and the tinctorial properties of the bacillus, to which allusion is made in von Behring's communication. The tubercle bacillus is difficult to stain and to decolour ; once coloured by the stain that suits it, the colour is retained, even under the action of a liquid acid capable of decolouring bacilli that do not possess the same fatty envelope ; hence the name of *acido-resistant* bacilli given to Koch's bacillus and to those having an analogous chemical composition.

In order to overcome this difficulty of absorption, an attempt was made to deprive the bacillus of its fatty matters ; but the desired result is attained only by means of rough physico-chemical actions, which profoundly change the living matter. When it was endeavoured to free them from the poisonous tuberculin, which is so injurious to the leucocytes, the "detoxicated" bacilli did not exhibit vaccinating properties. So long ago as 1897, the numerous experiments made with this object were summarized by Koch as follows : "We shall not succeed in habituating the organism to absorbing entire bacilli, which have been injected subcutaneously ; and by injecting small quantities of them we shall not habituate the organism to absorbing more."

Koch endeavoured to discover whether particles of bacilli would not be absorbed more readily than entire bacilli. From powdered bacilli, pulverized in an agate mortar while living and virulent, he obtained the new tuberculin, TR.[1] It was found possible to bring the pounding processes to such a state of perfection as to yield a powder devoid of acido-resistant properties, which showed that the texture of the bacillus must have undergone profound modification. These microbic products did not, however, exhibit immunizing properties. Koch's discouraging verdict, after numerous experiments, is that : "We shall never obtain better results with non-living bacilli."

[1] Abbreviations of this kind have long been employed in order to designate various microbic substances : they were made use of again in von Behring's communication to the Paris Congress.

The object to be achieved, then, was to modify the virulence of the tubercle bacillus, as Pasteur had modified that of the bacillus of anthrax. Pasteur's method of attenuating virus is based upon the plasticity of microbes. A virus is attenuated by cultivating it at an abnormal temperature, by allowing the cultures to grow old without transplanting them, or by exposing them to the action of certain chemical agents. From the old experiments of Grancher and Hippolyte Martin, which were in their time an innovation, to those of Lévy, of Strasburg, who believed that he could attenuate the bacillus by the action of glycerine, all attempts of this kind have miscarried. When the tubercle bacillus is being dealt with, senescence of a few months is nothing; we have to reckon by years. At the Pasteur Institute in Paris investigations have been made upon a variety of bacillus which appears to have lost its virulence in the space of twelve years. This attenuation, which indeed is slight, is but a commencement; it remains to be seen whether, when its action on a particular species of animal is known, we shall be able to draw conclusions from this as to what would happen in the case of man.

Since we do not possess a method of attenuating the tubercle bacillus, there is as yet no vaccination against tuberculosis by Pasteur's system. Can we hope for a Jennerian vaccination, and shall we find, under natural conditions, bacilli the virulence of which would be to that of the bacillus of human tuberculosis as the vaccinal virus is to the virus of small-pox? Shall we find, ready made in Nature, some bacillus which shall be the vaccine that we are unable to fabricate?

There are other kinds of tuberculosis than that which affects human beings; tuberculosis is found in cattle, horses, birds, reptiles, batrachians and fishes. There are, too, everywhere in Nature, on the blades and stems of grasses, in dunghills, and even in water, bacilli which possess the structure and the "acido-resistance" of the human tubercle bacillus.[1] These species of bacilli differ in virulence; the virulence of a bacillus is dependent upon the species of animal into which it is

[1] Crouzon and Villaret, "Les bacilles pseudo-tuberculeux," *Revue de la Tuberculose*, July, 1903.

inoculated, and that serves as a reagent. The bacillus of cattle, or bovine bacillus, is more virulent to the guinea-pig than the human bacillus, which is itself highly virulent; the human bacillus is less virulent to the rabbit than the bacillus of birds, or avian bacillus. The parrot is equally sensitive to the avian and to the human bacillus; the mouse is more sensitive to the bacillus of birds than to that of man.

At the Berlin Zoological Gardens, Madame Lydia Rabinovich has made *post-mortem* examinations of forty-five monkeys which had died from spontaneous tuberculosis. In twenty-seven of these cases it was possible to make a complete study as regards the anatomical lesions and the culture and virulence of the bacilli, and it was found that the tuberculous affections of the monkeys were caused by species or varieties of bacilli, which differed widely in the various cases. In nineteen cases there were found only human bacilli; in three cases only bovine bacilli; in one case there were bacilli of the human type in the lungs, and of the bovine type in the spleen; in two cases the bacilli were intermediate between the human and bovine types; in one case there were only bacilli of avian tuberculosis; in another there were forms intermediate between the avian and human types. It is not always easy to classify bacilli, and, in consequence of these difficulties in classification and the existence of intermediate types, Madame Rabinovich believes that there is in reality but one tubercle bacillus, which, through adaptation to different species of animals, develops into different varieties.[1]

As the result, however, of observation and experiment, three great classes of tuberculosis and tubercle bacilli have at length been distinguished: those of mammals, those of birds, and those of cold-blooded animals. They form as regards the human species, which possesses the most interest for us, a descending gamut of virulence; and, even lower down in the scale than the bacilli of cold-blooded animals (snakes, frogs, and fishes) there is also the host of "acido-resistant" bacilli, occurring in all kinds of situations, so little virulent to the guinea-pig that they cannot even be termed pathogenic, and comprised in the category of pseudo- or paratuberculous bacilli.

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[1] *Deutsche medizinische Wochenschrift*, May 31, 1906.

We may set ourselves a pretty philosophical problem by enquiring whether, in this multiplicity of species, some relationship is to be found, and whether the pathogenic bacilli of mammals, for instance, are not bacilli which were formerly innocuous and became progressively adapted to the organism of animals, which are to-day paying for their evolution. In other words, we may ask ourselves whether the intellectual acuteness of a Darwin might not discover the ancestor of the tubercle bacillus of our race in some bacillus which primitively vegetated upon grass, became accustomed to the organism of herbivores through being swallowed by them with the herbage upon which they browsed, and passed from the herbivores to man with milk, butter, and cheese, at or even before the epoch of the patriarchs and nomadic tribes.

Attempts have been made to verify this transformation or these *mutations* of tubercle bacilli by producing them in laboratories; bacilli of warm-blooded animals have been inoculated into cold-blooded ones, and *vice versâ*; and their virulence and toxicity have been compared before and after these attempts at artificial adaptation. The bacilli, however, were found to have retained the properties that they possessed at the outset, and, whether virulent or not to their new host, they were not modified. No human bacillus introduced into reptiles or batrachians has ever acquired *vaccinating* properties, as regards the normal human bacillus, like those of vaccinal virus with regard to the virus of small-pox. It is true that the first experimenters declared that they had obtained transformations of human bacilli into bacilli of cold-blooded animals in the case of the frog, but this was a mistake, which was explained shortly afterwards. They had sown human bacilli and reaped bacilli of cold-blooded animals, or simple "acido-resistants," but the latter did not originate from the human bacilli. They were non-pathogenic parasites, or *saprophytes*, which had passed from the water or plants in aquariums into the organisms of lizards or frogs; or bacilli which had been living in the frog all the time without doing it any harm (experiments by Herzog, Weber and Taute). It may happen that for once in a way a human bacillus causes a few tuberculous lesions in a reptile, but for all that it does not become transformed into a bacillus

of the type of those of cold-blooded animals (experiments by Bertarelli, 1905 ; and by Sorgo and Suess, 1907).[1]

The fixity of the principal types—bacilli of mammals, bacilli of birds, bacilli of reptiles, batrachians, and fishes, acido-resistant bacilli—is maintained. But could not Nature, which allows itself centuries in which to work, have done what we are incapable of performing in our laboratories ?

Among the multitude of tubercle bacilli, it has been sought to find a vaccine for man. Grancher and Hippolyte Martin were the first to endeavour to vaccinate the rabbit against avian tuberculosis with human tuberculosis, and Richet and Héricourt attempted to vaccinate the dog against human tuberculosis with avian tuberculosis. In 1904 Friedmann announced that he was vaccinating cattle by means of a bacillus isolated from a tortoise, suffering from spontaneous tuberculosis, in the Berlin Zoological Gardens. The promise held out was a splendid one, but silence followed, and the investigator's triumph was short-lived. Professor Möller vaccinated himself with a bacillus obtained from a slow-worm, and, in order to put his immunity to the test, inoculated himself in the veins—a dreadful experiment—with human tuberculosis. Möller has not become tuberculous ; would he have become so without the supposed vaccination with the bacillus from the slow-worm ? No good experiment without a control, say the upholders of the experimental method, and we ought to have had two Möllers, one vaccinated and the other not ; but it will readily be understood that these sensational experiments are not popular.

At the present time it appears to be established that the paratuberculous bacilli and those of cold-blooded animals cannot be vaccines for man, since they are neither virulent nor toxic to human beings ; a vaccine must be a virulent microbe. In the case, however, of a guinea-pig or rabbit, the animals generally used for experiments, the virulent microbe kills and does not vaccinate ; every virulent microbe is not a vaccine.

It therefore seemed useless to look for a Jennerian vaccination ; and when, in 1901, von Behring announced that he was vaccinating cattle against bovine tuberculosis by means of

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[1] *Centralblatt für Bakteriologie*, Orig., Bd. xliii., March, 1907.

bacilli of human origin, and that for the bovine species he had discovered the "jennerization" of tuberculosis, his communication was received with a certain amount of scepticism.[1]

Von Behring's method is based upon the fact that the human tubercle bacillus does not kill cattle, but vaccinates them against bovine tuberculosis; the human virus is a vaccine for the bovine species. It is on account of this relation between species and species, discovered by Jenner in the case of smallpox and vaccinia, that von Behring employs the expression "jennerization of cattle." It follows, therefore, that there are several kinds of mammalian tuberculosis, and that human tuberculosis and bovine tuberculosis are caused by two different species of bacilli. The idea of this diversity of species was brought before the scientific world by Robert Koch. At the Congress held in London in 1901, in a sensational communication, Koch stated that cattle are refractory to human, and human beings refractory to bovine tuberculosis; and from this he drew the practical conclusion that it is useless to spend so much money in providing for the sanitary inspection of animals, and of meat exposed for sale.

The first proposition, namely, that human bacilli are innocuous to cattle, was the easier to verify experimentally. Koch's experiments were repeated on all sides, and calves, cows, and pigs were inoculated with bacilli derived from human beings. In by far the majority of cases the animals did not succumb; in the small number of instances in which they were attacked with fatal tuberculosis, this was due to their having been inoculated with bovine bacilli, taken from human beings it is true, but communicated to them in milk or butter from cattle; the bacilli of human origin pathogenic to the animal were derived from intestinal or mesenteric tuberculosis (*tabes mesenterica*) of infants. It is therefore true that human bacilli do not kill calves; but these very experiments corrected the radicalism of Koch's ideas upon the other point, for it is by no means so certain that the bovine bacilli do not cause man to become infected with tuberculosis.

With reference to these questions, where what might be termed *experimental statistics* comes in, we never possess a

[1] *Lecture pour le prix Nobel*, Stockholm, December 12, 1901.

sufficiency of experiments, although fresh ones are made without fail every time that an opportunity presents itself, which is not so often as might be imagined. The investigator must have simultaneously at his disposal bacilli removed from the abdominal lymphatic glands of children and adults, and cattle, that is to say, cowsheds which will render it possible to isolate these animals for several months ; there are not many laboratories which possess such facilities.

In order to verify the second proposition, that bovine bacilli are innocuous to man, since we cannot inoculate human beings with cultures of bovine tuberculosis, we are obliged to have recourse to clinical observation. Milk and butter sometimes contain living and virulent bovine bacilli ; were these pathogenic to our species, thought Koch, all humanity would be attacked with tuberculosis contracted through food. This tuberculosis would be at first intestinal, and infants, whose nourishment is almost exclusively milk, would suffer most. *Primitive* intestinal tuberculosis in infants appeared to him, however, to be rare. In the archives of the Charité Hospital in Berlin, Koch was only able to discover five cases of it in ten years ; writing of 933 autopsies on children, Baginsky does not mention a single case, and Bieder met with only sixteen cases in 3,104 autopsies. Again, it has not been proved that these cases of intestinal tuberculosis in infants are caused by bovine bacilli ; instead they may be due to a secondary extension into the intestine of pulmonary tuberculosis of the human type. When, however, cattle are inoculated with bacilli of infantile tuberculosis, the animals frequently suffer from a serious attack of the disease. On this point we cannot share in the confidence displayed by Koch. The cases of tuberculosis produced in human beings by bovine bacilli are sufficiently numerous to justify the maintenance of a force of sanitary police for the purpose of exercising supervision over the animals that supply us with milk.

Eber recently inoculated calves with seven strains of tubercle bacilli taken from the abdominal glands of children who had died from various diseases ; in five cases out of the seven the bacilli proved virulent to the animals. Two of the cases observed by Eber are particularly interesting, in that the bacilli pathogenic to cattle were removed, not from intestinal

glands of children, but from the lungs of adults suffering from pulmonary phthisis.[1]

The English Commission charged, after the London Congress of 1901, with the task of submitting Koch's statements to experimental verification, came to the conclusion that human beings can be infected with the bovine bacillus, and that cow's milk may give tuberculosis to man. Out of sixty cases of human tuberculosis, which were subjected to minute investigation, fourteen were due to bovine bacilli. Again, out of these sixty cases, there were twenty-two in which the disease was certainly of alimentary and intestinal origin, and thirteen of these twenty-two cases were due to bovine bacilli. It is even stated that bovine bacilli were found in lesions of the lymphatic glands of the neck.[2]

The English Commission does not believe that the human bacillus can become transformed into the bovine bacillus and *vice versâ*, and it acknowledges that there are two relatively stable varieties, which is in accordance with the ideas of Koch. This allows us to think that the danger from bovine tuberculosis is of a limited character; it is evident that if the bovine bacillus could readily become changed into the human type in man, and conversely, there would, on the contrary, be no bounds to the danger. The English experiments clearly show the basis of truth underlying Koch's doctrine.

Weber has found the bovine bacillus in fourteen out of seventy-eight cases of human tuberculosis; this investigator, who is a pupil of Koch, therefore allows that bovine tuberculosis is dangerous to man,[3] but he adds quite rightly that the danger is limited. Infection with bovine bacilli takes place only through food (milk); it is scarcely met with except in infants, and very simple reasoning is sufficient to show that it is rare; as a matter of fact, it attacks young subjects, at the age at which there are fewest deaths from tuberculosis. According to the statistics of Cornet, which cover a period of sixteen years, the mortality from tuberculosis is at its minimum between the ages of 3 and 15—when infection with bovine

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[1] *Beiträge zur Klinik der Tuberkulose*, Bde. iii. and v.

[2] *Journal of Comparative Pathology and Therapeutics*, vol. xx., March, 1907.

[3] *Deutsche medizinische Wochenschrift*, December 6, 1906.

bacilli is most to be feared—and at its maximum after 20 ; it is therefore almost exclusively due to the human bacillus.

From a theoretical point of view, Koch's assertion remains true as a whole, but it requires to be modified. A human type and a bovine type of tubercle bacillus do indeed exist, but these are not two absolutely distinct species ; it would be more correct to term them natural varieties, which have been produced by a prolonged series of adaptations to particular species of animals. Between the two definite types we have intermediate varieties, which may be virulent to a certain extent both to cattle and to human beings. A bacillus is not altogether defined by its origin ; it is only by making experiments upon animals that we can determine its properties, and especially its pathogenic power.

When von Behring set himself to discover whether the human bacillus, which does not kill cattle, was capable of vaccinating them against bovine tuberculosis, he at once placed himself in a better position than those who had studied antituberculous vaccination before him. Instead of dead microbes, he employed living ones ; and instead of non-virulent living microbes, he used microbes which were virulent but not lethal to the species of animal selected.[1]

In vaccination against anthrax, Pasteur's two vaccines are inoculated at an interval of a fortnight, since immunity to an acute disease is rapidly acquired. On the other hand, in the case of tuberculosis, which is a chronic disease, it was found by von Behring and Koch that a much longer period of time is necessary ; the preparatory inoculations must be made at intervals, not of a few days, but of several months. It is just these conditions of time that render tuberculosis experiments difficult and costly ; for, since distant consequences of the vaccinations have to be taken into account, the animals used for the experiments must be housed, fed, and kept under observation for years. An experiment with a group of cattle on the lines of von Behring's investigations costs from £1,000 to £1,200.

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[1] The majority of von Behring's papers on tuberculosis have been published in his *Beiträge zur experimentellen Therapie ;* see also his *Moderne phtisiogenetische und phtisiotherapeutische Probleme*, &c., Marburg, 1905.

In von Behring's vaccinations, the detail that required the greatest care was the choice of the microbe to be used as vaccine ; it was not a case of taking the human bacillus nearest to hand, since every human bacillus is not a vaccine for cattle. The bacillus selected by von Behring is one with which he has made manifold experiments since 1895 ; this is the celebrated *bovovaccine*, which produces in the calf a local disease, which does not become generalized.

Bovovaccine is a powder composed of bacilli which, though desiccated, are alive and virulent. It has been proved by repeated experiments that this vaccine does not kill cattle ; it is not retained in the body of an animal, so that it is capable, for instance, of passing later on into the milk and returning to man. A few days after inoculation it is no longer to be found in the blood of calves, and between vaccination and the time when the cows are used for milking purposes a year and a half or two years elapse. Healthy calves aged from a fortnight to three months are selected for vaccination ; the inoculation is made in one of the large veins of the neck, and the first injection contains 4 milligrammes of dry bacilli ; the second, which is performed after an interval of three months, contains 20 milligrammes.

Bovovaccine, according to von Behring, has a definite standard of virulence, which has not varied in ten years. There is no risk of its working itself up, and causing a fatal attack of tuberculosis in the calf, nor of its becoming attenuated and eventually inactive, like a paratuberculous bacillus. Its virulence is the subject of incessant supervision, and the same care is bestowed upon every bacillus employed as a vaccine. There can, however, be no doubt that it is not so difficult as von Behring maintains to find a bacillus that possesses the same immunizing properties; the further we advance in the practice of this vaccination, the easier does the immunization of cattle appear.

Von Behring's method was at once confirmed by experiments made in all countries ; the earliest of these were those of Thomassen, in 1902 ; the most recent, those of Vallée and Rossignol, at Melun, in 1906. The results obtained by the last-mentioned investigators were stated to be as follows : Vaccinated calves resist both natural and experimental infection, and

remain immune when kept in sheds in which other cattle, suffering from advanced tuberculosis of the lungs, distribute in coughing bacilli which are fatal to the non-vaccinated; they even prove resistant when inoculated with cultures of bovine tuberculosis. This method of immunizing calves is widely adopted for practical purposes, since animals treated in this way remain free from the disease until required for slaughter, so that there is no danger to human beings through either their milk or their flesh. By abolishing bovine tuberculosis, von Behring's antituberculosus jennerization should suppress one of the sources of infection to which human beings are exposed.[1]

Here, then, towards the middle of the year 1906, there was reason to believe that certain truths had been established. Instead, however, of eating the vaccinated animals, particular care was taken to keep them under observation, in order to discover whether they would remain free from the disease. This was a wise precaution, the consequences of which we shall see.

If the human bacillus is a vaccine for cattle, why should not the bovine bacillus be a vaccine for man? The question is one which would soon be decided, were it permissible to make experiments upon human beings.

It will, perhaps, be remembered that following upon Koch's communication to the London Congress, Dr. Garnault inoculated himself subcutaneously with bovine tuberculosis, in order to prove that, contrary to the opinion of Koch, the bovine bacillus is pathogenic to man. The experimenter contracted certain local lesions, which he caused to be extirpated before it was possible to tell whether they were likely to become general and to lead to an attack of pulmonary tuberculosis. No definite conclusion could be drawn from this experiment.

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[1] The reader who consults von Behring's writings will think it strange that this investigator does not admit that human and bovine tuberculosis are, as was proved by Koch, due to two distinct bacilli, since this would appear to be the foundation of his vaccination of cattle. A "unicist" like von Behring, however, once he has to admit that there are varieties produced by adaptation, extends his hand to a "dualist," who knows that species have not an absolute value. Koch, for his part, has vaccinated cattle with success; and theoretical discussions as to the value of specific distinctions lose their significance in the presence of actual facts.

The same experiment has recently been performed by a German scientist, Dr. G. Klemperer, with the opposite intention of showing that the bovine bacillus is no more fatal to man than the human bacillus is to the ox—a necessary condition of an antituberculous jennerization for the benefit of human beings. When inoculated subcutaneously in the arm, the bovine bacilli merely produced a local tuberculous lesion, which after ten months had not extended further. A colleague of Dr. Klemperer, who was known to be suffering from tuberculosis, and consented to receive fourteen inoculations with bovine bacilli, not only experienced no ill-effects, but even appeared to derive some benefit therefrom.[1]

Kleine has applied himself to the study of tuberculomata, or tuberculous lesions of the skin which are often found in men who handle meat in abattoirs. The five subjects whom he had under observation were otherwise in perfectly good health, and none of their glands were infected. The tuberculomata of the skin had already lasted for years (in one case for eight years), without extending to the lungs or being in any way prejudicial to the general health. Since they all contained bovine bacilli, these facts point to the same conclusion as that which is to be deduced from Klemperer's experiment. Kleine remarks that, in the case of man, not a single reliable instance is known of cutaneous infection by the bovine bacillus having become generalized.[2]

When, however, we remember that the anthropoid apes are closely related to man, we shall find little to reassure us in the experiments made by von Dungern in Sumatra upon two species of gibbon, the siamang (*Hylobates syndactylus*), and the unko (*Hylobates agilis*). These monkeys proved equally susceptible to inoculation by bovine and by human bacilli.[3] The monkeys infected by way of the alimentary canal exhibited abdominal lesions similar to those of infants suffering from intestinal tuberculosis, as the result of being fed with contaminated milk. We are strongly inclined to believe that, as regards the two species of bacilli, man would behave in

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[1] *Zeitschrift für klinische Medizin*, Bd. lvi.

[2] *Zeitschrift für Hygiene*, Bd. lii., 1906.

[3] *Münchener med. Wochenschrift*, January 2, 1906.

precisely the same way as an anthropoid ape. Yet, with reference to these experiments, there is perhaps a reservation to be made ; it is possible that gibbons, especially when kept in captivity, are more susceptible than man to all kinds of tuberculosis, and constitute a "reagent" too sensitive to show differences, which appear with greater distinctness when more resistant mammals are chosen as subjects for experiment.

It must be understood that von Behring did not think that it was possible for him to make experiments upon human beings, and especially upon children, in order to test the action of any virulent tubercle bacillus whatever. "It will readily be admitted," said he, at the Congress in Paris in October, 1905, "without there being any necessity for me to dwell upon the fact, that I have considered all the possibilities of applying this process to the campaign against human tuberculosis. My experience, however, has led me to decline altogether to introduce into the human body, for a therapeutic end, living tubercle bacilli."

Von Behring was obliged to revert to the study of the products extracted from tubercle bacilli, with new ideas suggested by the success of bovo-vaccination. In the same communication, the sibylline appearance of which is due to its extreme conciseness, he mentioned a product which retains the biochemical properties of the living bacilli. "This new curative principle," he stated, "plays the essential part in the immunizing action of bovo-vaccine." The most suggestive lines are those in which von Behring makes a very guarded allusion to the intervention of living cells in the elaboration of the substance by which human beings are to be cured. We are told that the tubercle bacillus, after being inoculated into animals, is acted upon, modified, and altered by the tissues with which it lives in a state of symbiosis, and it is proposed to extract these tissues in order to utilize them for the benefit of man. Former investigators had already attempted to convert into a remedy the nodules produced by tuberculosis in the peritoneum and pleura of cattle, but it is a far cry from an ingenious idea to a practical success. Von Behring realizes this, and writes : "How long a time must still elapse before the discovery and utilization of my new remedy are justified by the results, I know not."

In the course of his investigations upon cattle, von Behring's fertile brain evolved an idea which altered our conceptions as to the origin of human tuberculosis, and quite recently gave rise to fresh therapeutic experiments.

Tuberculosis attacks the lungs because man inhales tubercle bacilli with the air ; such is still the accepted doctrine in accordance with which dry sweeping has been denounced, and a ruthless war declared against expectoration. Sputum, when dried, pulverized by being trodden under foot, and whirled into the air by the wind, or swept up by garments, is the great carrier of germs. That tuberculosis can actually be contracted by inhalation has been demonstrated by a series of admirable experiments, and Tappeiner infected dogs by spraying into their kennel water charged with bacilli. It was remarked by Koch that the depth to which the bacilli penetrate into the respiratory passages depends upon the way in which we breathe ; when we breathe deeply, and with the mouth open, they penetrate further ; but if we breathe through the nose, we have by so doing a certain guarantee against the penetration of infectious dust, since the nasal mucous membrane retains a considerable portion of it. Cornet suspended cages containing guinea-pigs on the walls of a room in which were beaten carpets soiled with dried sputa, and out of forty-eight guinea-pigs forty-seven became tuberculous. Straus swabbed out with sterile wool the nostrils of the clinical clerks and attendants in his hospital ward, and in nine cases out of twenty-nine the swabs were found to contain virulent bacilli. According to Flügge, in speaking, and especially in coughing, people emit minute droplets of saliva, which are capable of "spraying" the tubercle bacillus to a distance of two metres. These observations prove that droplets and dust are dangerous, but after all they do not prove that the germs contained therein penetrate directly to the ends of the bronchi.

It was not believed that tuberculosis is contracted through alimentation, and Koch, who denied it, argued that tuberculous lesions of the intestine are extremely rare. People forgot the old and remarkable experiments of Chauveau on "the virulence of tuberculosis resulting from the introduction of tuberculous matter into the digestive tract."[1] Intestinal tuberculosis was

[1] *Bulletin de l'Académie de médecine*, 1868.

regarded rather as an extension of pulmonary tuberculosis, and it was thought that tuberculosis did not invade the organism by way of the intestine, since lesions marking its passage are not found in the latter.

Nevertheless there are many facts which prevent us from believing that the bacilli penetrate directly into the lungs ; the continual movement of the vibratile cilia that clothe the mucous membranes, the secretions ejected in coughing, and an extremely active phagocytosis maintain throughout the respiratory tract a vigorous defence, which protects the alveoli. It is now a long time since it was first thought that the germs penetrate by way of the vascular or lymphatic systems, rather than the air passages, and that excoriations of the nose, mouth, and throat would serve as ports of entry. Within the last year or two, Wrzosek, of Cracow, who resumed, with greater precision of technique, the experiments that consist in infecting animals by spraying microbes into the air breathed by them, showed that the microbes do not penetrate into the lung if the respiratory passages are in a sound condition, but do so only if, at the time they are inhaled, there are lesions in the trachea and bronchi.[1] In the former case, they are destroyed in passing through the bronchi, and do not travel so far as the alveoli ; in the latter, they do not penetrate by way of the respiratory organs, but by that of the blood stream. When it was intended to make an inoculation in the respiratory tract, the operation was in reality performed in a blood-vessel ; by means of artificial or natural rents, the bacilli reach the veins and the right side of the heart, and pass thence to the lung, where they are distributed at the moment when the blood spreads out into a thin sheet in order to submit to the action of the oxygen in the air. Pulmonary tuberculosis would therefore appear to be an effect of the pulmonary, or lesser circulation.

There is, however, another channel by which the germs may be conveyed to the heart and lungs, and this is formed by the digestive and intestinal tract. Lymphatic ducts and veins form connections between the intestine and the heart, and it is by means of these that the juices from digested food

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[1] *Bulletin de l'Académie des Sciences de Cracovie*, January, 1906.

pass into the blood. According to von Behring, tuberculosis through alimentation is much more common than tuberculosis through inhalation; and, in the guinea-pig, the so-called inhalatory type of tuberculosis (pulmonary tuberculosis) can be experimentally produced, when access to the aerial channels is closed to the bacillus. Three statements, which should not be separated from each other, are warranted by von Behring's thesis :—

Firstly, pulmonary tuberculosis can be contracted through the alimentary canal. Experiments by Calmette and Vallée [1] have confirmed those of von Behring; in the case of goats, it was found that feeding the animals a few times with forage to which virulent bacilli had been added led to an attack of pulmonary tuberculosis, which was rapidly fatal to the animals; and a single infectious meal sufficed to render guinea-pigs tubercular. The mode of inoculation by which the glands connected with the lung are most surely infected is ingestion.

Secondly, it is above all in the case of young animals that tuberculosis penetrates by way of the intestine; and, since no intestinal lesion remains as evidence of its passage, the rarity of such lesions is not an argument against alimentary tuberculosis, and on this head nothing is left of the objections of Koch and his pupils. While the intestinal mucous membrane of the adult is rendered almost impermeable to microbes by a continuous coat of mucous substance, the latter, according to von Behring and Disse, is absent, insufficient, or discontinuous in young animals, so that bacilli easily pass through. No lesion is formed, precisely because the bacillus is not arrested; there is penetration, but nothing in the shape of rupture.

Lastly, tuberculosis contracted through the intestine during youth may develop tardily after remaining latent for a long time. It has been observed by veterinary surgeons that calves are found to suffer from tuberculosis of the abdominal glands, which are attacked by the bacillus after it has passed through the intestinal mucous membrane, while tuberculosis in adult cattle is almost always pulmonary. It is the same in the case

[1] *Comptes Rendus de l'Académie des Sciences,* and *Comptes Rendus de la Société de Biologie,* 1905-7.

of the human species; but the bacilli have travelled without attracting attention, and have remained for a long time dormant in the glands before attacking the pulmonary tissue. Pulmonary tuberculosis in the adult arises from intestinal tuberculosis in the nursling.[1]

To the experiments that are direct proofs, MM. Vansteenberghe and Grysez, pupils of Calmette, have added an indirect demonstration, by means of their ingenious researches upon pulmonary anthracosis,[2] which is the name bestowed upon the impregnation of the lungs by coal-dust floating in the atmosphere of towns, factories, engine-rooms, and especially mines. That this dust penetrates into the lungs with the air that we breathe has never been doubted; nevertheless it would appear to be with coal-dust as with the tubercle bacillus—we swallow but do not inhale it. The dust reaches the lung by passing through the wall of the alimentary canal. In animals killed after a course of breathing lamp-black, we find black in the nose, mouth, throat, and as far as the œsophagus, but never in the trachea, bronchi, or lungs. Dust invades the lung directly only when we breathe too heavily, that is to say, when we place ourselves in conditions which have nothing in common with a natural state of things; and even with rabbits, which appear to breathe solely through the nose, we do not always succeed. Experimental anthracosis obtained by inhalation resembles that produced by feeding so closely that it must be attributed to the particles of carbon swallowed rather than to those drawn in with the breath. The demonstration was carried further, and rabbits in which the œsophagus had been ligatured or obstructed were caused to inhale lamp-black for a prolonged period; their lungs remained free, while the black penetrated the lungs of other rabbits which had not been interfered with. Again, rabbits in which one of the two large bronchi had been plugged were made to inhale in the same way; the lung separated in this way from the external atmosphere by a plug, which forms a filter impermeable to dust, became anthracosed like the free lung. By aid of the microscope, the particles of

[1] Von Behring, "*Tuberkulosebekämpfung*," a lecture delivered before the Congress at Cassel: *Deutsche medizinische Wochenschrift*, September 24, 1903.

[2] *Annales de l'Institut Pasteur*, t. xix., 1905.

carbon were found, not deposited upon the walls of the bronchi, but enclosed in the cells of the pulmonary tissue. Thus pulmonary anthracosis, like pulmonary tuberculosis, is contracted through intestinal absorption.

If von Behring's idea be correct, doctors who perform numerous autopsies ought to find very few tuberculous lesions in children, and to find more according as the subjects have died at a more advanced age. This is, indeed, the purport of the figures given by Naegeli, who, in some thousands of autopsies, did not meet with a single human cadaver of more than 39 years of age that was free from tuberculous lesions. According to the statistics in question, there are lesions, whatever be their situation, in 96 per cent. of individuals aged from 18 to 30 ; in 50 per cent. of adolescents of from 14 to 18 ; in 33 per cent. of children of from 5 to 14 ; and in 17 per cent. of children from 1 to 5 ; in infants under 1 year, he was not able to discover tuberculous lesions with certainty. We know that these lesions are infallibly revealed by the tuberculin test, and in ninety-six infants to whom this test was applied Berend did not obtain a single case of positive reaction. Thus we may conclude that what penetrates by way of the intestine is not tuberculosis, but only the bacillus ; tuberculosis, the chronic reaction of tissues to the microbe, is not set up until later.

These facts in no way alter the rules for the prophylaxis of the disease. Dust is always dangerous in consequence of the bacilli contained in it ; but, according to Calmette's formula, it is dangerous, not because we inhale, but because we swallow it.

The alimentary canal is, therefore, a channel for tuberculosis infection, and von Behring asked himself why it should not also be a channel for immunization. In the milk of cows rendered immune to tuberculosis there must be immunizing substances ; by adding traces of formol to the milk, the bacilli that it may contain would be rendered innocuous, without injuring the elements that constitute its nutritive value, or the vaccinating substances elaborated in the organism of the cow. Milk so treated was experimented with at Marburg, but the results do not seem to have been successful, though the attempt led to the formulation of useful rules for aseptic milking, and the aseptic treatment of vessels used for the storage and distribution of milk.

In France, Roux and Vallée on the one hand, and Calmette and Guérin on the other, have sought to produce, by the alimentary channel, the vaccination performed by von Behring by means of intravenous inoculation.[1] By supplying calves with food impregnated with human bacilli, they were rendered immune to bovine bacilli subsequently administered to them in a similar manner. Immunity by way of the alimentary canal, however, is slower in establishing itself, and it may be that it is also neither so thorough nor so permanent.

The same experimenters found that calves could be vaccinated by way of the alimentary canal, even with bacilli that had been killed, and from this Calmette was led to make a very bold sugestion. Why, he asked, should we not attempt to vaccinate infants by mixing dead tubercle bacilli with their milk? After its vaccinating meals it would only be necessary to guard the child against any possible risk of tuberculous contagion, during the time necessary for the acquisition of immunity. Special dairy farms should be established for the supply of milk during the first and critical period of life.

We have, however, not yet got so far as this; it is possible, but not certain, that infants can be vaccinated like calves. Cattle are, as regards tuberculosis, highly susceptible and easy to vaccinate; they are, so to speak, on the border-line, and by a therapeutic intervention we can readily direct them towards the side on which health lies; we have reasons for believing, but not for being certain, that the human species enjoys the same privilege. How can this be ascertained without risk? Calmette has recently published some experiments which tend to show that the ingestion of small quantities of tubercle bacilli, even when killed, is harmful to organisms, even though in good health. In short, the alimentary method is not the most desirable way of making a vaccination, but rather a last resource; we are not sure about what a calf or an infant swallows and absorbs. A transitory affection of the digestive tract, even though mild and unsuspected, may change all the conditions; and we do not know the value or the degree of the immunity that can be acquired in this way. We have a basis of experiment sufficient to enable us to condemn suspected milk, and to

[1] *Comptes Rendus de l'Académie des Sciences*, t. cxlii., June, 1906.

declare that alimentary tuberculosis exists and is even a frequent mode of infection in man ; but it does not yet justify the practice of alimentary vaccination. There is, however, nothing to prevent a new discovery, which will render Calmette's idea a practical one. Theoretically the idea is sound ; vaccination by ingestion may be that which provokes the most extensive reaction of the lymphatic glands, and of the phagocytic means of defence.

Suppose a child to have been treated in this way ; he must be kept under observation for twenty years, and, if he does not become tuberculous, this in no way proves that he owes his immunity to the treatment ; if, on the other hand, he does become tuberculous, it is not a proof that the treatment is valueless : the child may have acquired a measure of immunity too slight to withstand a severe attack, or of too short duration to resist subsequent infection. For experimental purposes it would be necessary to apply the treatment to a whole generation, but this would entail no small amount of risk. In the case of cattle the problem is to keep them free from the disease until the day, never very distant, when they are used for food ; in the case of human beings, however, a longer period of immunity is required. Experiments can be made upon anthropoid apes, but conclusions as regards human beings in temperate climates cannot yet be drawn from the chimpanzees of Equatorial Africa, especially considering the very short time that these animals can be kept in captivity. In this connection we can hardly fail to remember that it was suggested by Pasteur that criminals condemned to death should be reprieved, in order to be used as the subjects of experiments, which would not be certainly fatal to them, but would benefit all mankind.[1]

All methods of preventive vaccination encounter the same difficulties, and for this reason the true problem before us is to cure tuberculosis in its first stage. Antituberculous vaccination of cattle would render it possible to stamp out, by means of alimentary hygiene, the chief source of danger to human beings, and it suggests fresh therapeutic attempts, from which man will benefit. The last word has not yet been said : it remains to discover whether, in consequence of their

[1] R. Vallery-Radot, *La vie de Pasteur*, p. 579.

immunity, vaccinated cattle can be treated in such a way as to furnish, with their serum, the remedy that we have not yet succeeded in obtaining. The question is now being studied.

"In the matter of tuberculosis, prophylactic hygiene is more powerful than any therapeutics." Such were the pessimistic words of the illustrious scientist to whom we owe the discovery of the tubercle bacillus and tuberculin, but such pessimism is not final. Science has not only created anti-tuberculous hygiene, but has just discovered new therapeutic effects. There is the greater reason to hope that man is an animal, naturally susceptible, but also naturally resistant to tuberculosis, if it be true that tuberculous lesions, whether extensive or microscopic, active or cicatrized, exist in 70, and even, according to the statistics of Naegeli, in 98 per cent. of our fellow-creatures! The organism and the bacillus come to terms with one another; the bacillus becomes dormant, or dies. Even before the discovery of Koch's bacillus, there were observed in the glands of scrofulous persons strange bodies, the significance of which was not understood until later, but which are nothing else than dead and disintegrated tubercle bacilli. Metchnikoff has drawn attention to these cases of spontaneous cure, the causes of which he was the first to elucidate.[1]

By means of the natural resources of the organism, tuberculosis is already curable: this is not a paradox, but a fact. It is certain that experimental medicine will find the remedy, whether preventive or curative, that will act in the same way as Nature.

II.

A few months have gone by, and in the interval the hopes that had been based on the antituberculosis vaccination of cattle have considerably diminished.

The work of the laboratories has dealt with the same subjects: the vaccination of cattle, and the channels by which the tubercle bacillus makes its way into the organism. These two questions are connected, since milk is the principal

[1] *Leçons sur la pathologie comparée de l'inflammation*, p. 193.

carrier of tuberculosis, which is contracted by way of the alimentary canal.

At the International Tuberculosis Conference, held in Vienna in September, 1907, and at the Berlin Congress on Hygiene and Demography, which took place at the end of the same month, there was much talk of channels of infection, but silence on the subject of bovovaccination. The former question remains open ; the latter appears for the present to have ended in disillusion, though perhaps there is still room for hope.

The story of bovovaccination may be summed up in that of the experiment at Melun, which was commenced in December, 1904, by Vallée and Rossignol, under the auspices of the Society of Practical Veterinary Medicine. Twenty calves were vaccinated by von Behring's method, and after the interval of three months laid down by the German scientist they received the second vaccination. They were then subjected to various modes of infection, some artificial and others more closely resembling those met with under natural conditions—virulent inoculation in the skin and in the veins, cohabitation with infected animals, or a sojourn in contaminated cattle-sheds. Non-vaccinated *controls* were treated in the same way, and finally autopsies were held and the organs were compared.

The first report by Rossignol and Vallée, published in March, 1906, was to the effect that von Behring's method was efficacious ; the second, issued in October of the same year, was much less positive.[1] Both were based upon ascertained facts, which had been carefully observed ; but the *time* factor had at first been taken too little into account, and time proved to be the decisive element in the case.

Three months after vaccination the calves were resistant to tuberculosis ; when eight months had elapsed they were still resistant ; a year after being vaccinated they were resistant no longer. If a certain immunity had been conferred by the vaccination, it was merely transient : indeed, it is scarcely permissible to speak of immunity ; vaccination produces a

[1] *Bulletin de la société de médecine vétérinaire pratique*, 1906.

more or less durable *resistance.* The second report by Rossignol and Vallée was as pessimistic as the first had been optimistic : its conclusions are as follows :—

(1) "Bovovaccine is a product of unequal virulence to the guinea-pig : it is therefore permissible to assume that its effects in the case of the ox are not always identical." It will be remembered that bovovaccine was said to be of uniform virulence.

(2) "The tolerably well-marked resistance *to intravenous inoculation*, exhibited by the vaccinated animals three months after treatment, becomes somewhat rapidly exhausted and, in certain subjects, disappears in a year." As we know, it was hoped at the outset that animals could be largely immunized for practical purposes, and would remain immune until required for slaughter, without either their milk or their flesh being dangerous to man.

(3) "The resistance of vaccinated subjects *to contagion*, such as results from contact in the stall with animals suffering from open tuberculous lesions, is but slight, and does not last more than a few months." It is, therefore, scarcely to be expected that bovine tuberculosis will be stamped out by the treatment.

A single experiment, even though so well conducted as that at Melun, is not sufficient, and there have been others. In every country, public authorities have had von Behring's method tested by scientific men of the greatest experience, and everywhere the conclusions arrived at have been the same as in France. Almost the only results that can be recorded as favourable are those obtained by Pearson and Gilliland, under the auspices of the Pennsylvania Live Stock Sanitary Board, and it must be admitted that these stand alone in their optimism.

In Italy we have had the experiments of Maffucci and Pepere,[1] who, so long ago as 1905, came to the conclusion that it is impossible to speak of immunity, but at the most of resistance. According to the authors in question, this resistance does not last ; it is liable to be shortened by incidents which form part of the normal life of the animals, such as parturition and suckling, and the virulent bacilli await within the organism

[1] *Annal. d Igiene Sperim.*, vol. xv., 1905.

the decline of this resistance, in order to resume their virulence and produce generalized tuberculosis.

Again, there was the experiment by Belfanti and Stazzi, at Mortara, under the direction of the Veterinary School of Turin,[1] which established a point which has been confirmed by other experiments; in the case of vaccinated calves, the diagnosis of tuberculous lesions by tuberculin has not the almost infallible value that we are justified in attributing to it in veterinary practice. Moreover, if, after vaccination there comes a moment when the animal possesses a certain resistance, there is *first* a period during which it is more susceptible to infection than non-vaccinated animals. This fact, which was also observed by Calmette and Guérin, entails the troublesome necessity of shielding the calves from risks of natural infection during the "vaccinal period." Vaccination therefore does not dispense with prophylactic measures.

In Belgium, experiments by Degive, Stubbe, Mullie, and Liénaux[2] (a commission appointed by the Department of Agriculture) resulted in the same conclusions as at Melun.

In Argentina, experiments have been made by Lignières,[3] of Buenos Ayres; in Bohemia, by Hutyra[4]; and in Germany, by Eber.[5] In the final test, these observers noted in several cases more extensive lesions in the vaccinated than in the non-vaccinated animals. Hutyra remarks that the vaccinated subjects show themselves still less resistant to infection through the alimentary canal than to inoculation in the veins, which is the opposite of what is required in practice. Von Behring's *bovovaccine* has not the unique value that was attributed to it; the same resistance is obtained with human bacilli of whatever origin. It is not indispensable that the operation should consist of the two intravenous inoculations prescribed by von Behring; a single subcutaneous inoculation, with fresh bacilli, is easier and is found to be even more efficacious.

Still more serious, however, from the point of view of the

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[1] *La Clinica Veterinaria*, anno xxix.

[2] *Annales de méd. vétérinaire*, February, 1906.

[3] *Bulletin de la soc. centrale de méd. vétérinaire*, 1907, p. 112.

[4] *Zeitschrift für Tuberkulose*, Bd. xi., Heft 2.

[5] *Centralblatt für Bakteriologie*, Bd. xliv., 1907.

preservation of human beings, are the following facts, observed by Vallée, by Lignières, and by Moussu.[1] Since the vaccinated animal is destined for use as food, there must only be introduced into its body products devoid of tuberculizing activity, and von Behring declares that bovovaccine is innocuous. In certain experiments by Vallée, however, the bovovaccine received from Marburg and inoculated into the guinea-pig (the animal regularly used for experimental purposes) showed itself innocuous as a rule, but nevertheless on several occasions gave rise to tuberculosis.

In animals which have been vaccinated, then tested by virulent inoculation, and after intervals previously agreed upon, slaughtered and submitted to autopsy, there are found lymphatic glands which in spite of their normal appearance contain living tubercle bacilli ; for these glands, when crushed and inoculated into the guinea-pig, cause it to become tuberculous. Whence come these virulent bacilli ? It was at first thought by Lignières that they were the bacilli that constitute the vaccine, but it has been shown by Vallée that they are those of the virulent or test inoculation. Imprisoned within the glands, they are scarcely exposed to the risk of being ejected with the saliva, or expectorated into the drinking-trough or manger in coughing ; they are not a source of immediate danger to man or to the animal host ; but their presence proves that the latter is incapable of absorbing them, and we are therefore led to dwell on this latent tuberculosis, which, though concealed by a transitory resistance, is ready to awake. Moussu justly remarks that in man cases of recurrence of active tuberculosis are occasionally observed *years* after the extinction of benign tuberculous lesions, such as a coxalgia. How, then, is it possible to believe in the permanent immunity of cattle, which retain in their glands living and virulent bacilli ?

It might possibly be objected that what was done at Melun, at Mortara, in Belgium, Argentina, Germany, and Austria, consisted after all of laboratory experiments on a large scale, and that under natural conditions animals are not subjected to such

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[1] *Bulletin de la société de médecine vétérinaire pratique*, May, 1906 ; *Bulletin et Mémoires de la soc. centrale de méd. vétérinaire*, July, 1906 ; *Recueil de méd. vétérinaire*, November, 1906.

severe tests. These experiments, however, were not all; through the exertions of von Behring and his pupils, and of impartial experimenters anxious only to establish the truth, vaccinations have been made on a large scale on farms, upon herds of cattle either at pasture or under cover.[1] These are already numerous enough to confirm the great experiments in the laboratories.

The state of health of vaccinated herds is ascertained by means of the tuberculin test; now it has been proved that the reaction to tuberculin loses its value in the case of cattle which have received the vaccine, whence there ensues a general uncertainty which overshadows the results. In the second place, there arises the question whether the herds remain subject to the prophylactic regulations known as Bang's system, the essence of which consists in ridding the herd of animals attacked by the disease. The Bang system has shown what it can do, and those who employ it are justified in claiming its share in the favourable results displayed by the statistics. In fact, according to the experiments already published, relating to two groups of animals of the same age and kind, and kept under the same conditions, the one group vaccinated and the other not, a year after the vaccination there is observed in both cases the same proportion of positive reactions to tuberculin, indicating tuberculous lesions.[2] In the cases in which bovovaccination was applied concurrently with Bang's prophylactic system, the results hardly exceed what have been produced by Bang's method alone. The failure of the experiments at Melun and Mortara hardly justifies us in attributing all the successes to vaccination; so that instead of regarding Bang's method as auxiliary to vaccination, it is, for the present, fairer to consider it as the essential factor, and bovovaccination as a subsidiary method, which has not yet proved its value (Hutyra's conclusions).

Ought we, then, to have recourse to repeated vaccinations, in the hope that, one following the other, they would produce a

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[1] Experiments by Schricker, Strelinger, Römer, Eber, Heymans and Mullie, Hutyra, &c.

[2] *In the case of vaccinated animals,* if negative reaction does not prove that there are no lesions, positive reaction proves that there are.

resistance which could be prolonged at will? Such a hope can scarcely be entertained, seeing that successive inoculations with bacilli render the organism *susceptible*, instead of immune. If, through fear of living bacilli, which are capable of existing for a long time in a latent condition in the vaccinated organism, it should be proposed to vaccinate with non-virulent bacilli, it must be remembered that such bacilli do not confer immunity.

From what has been stated above, it will have been seen that von Behring's bovovaccination, which was proposed in 1901, did not, in 1907, perform all that might have been expected of it. Science remains indebted to von Behring for a mass of experiments and observations, which will be the starting point for fresh attempts. A germ, so to speak, of vaccinal immunity to tuberculosis does indeed appear to exist; but for the moment there is not yet any such thing as serotherapy or vaccination of practical value.

Von Behring's idea that tuberculosis in the adult arises from the ingestion of tubercle bacilli during infancy is of such importance to medicine and hygiene, that a host of experiments has been made for the purpose of verifying the passage of the microbes into the blood and organs through the intestinal mucous membrane. The investigations have dealt, not only with Koch's bacillus, but with pathogenic microbes of all kinds, and even with non-pathogenic microbes and inert dust. The problem of the channels of access of the tubercle bacillus was but a particular case in a problem of general hygiene, which was, to decide to what extent infectious diseases can be caused by microbes which pass through the wall of the intestine. Von Behring's idea was in harmony with the views of Metchnikoff as to the *rôle* of the intestinal flora.

Vansteenberghe and Grysez, who are pupils of Calmette, have attempted to strengthen von Behring's hypothesis by experimenting with the particles of carbon found in smoke, coal-dust in mines, and Indian ink. Their experiments appeared to show that these particles, when ingested with food, pass through the wall of the intestine into the mesenteric glands, and thence, by way of the great lymphatic ducts, into the vena cava, the heart, and finally into the lungs. This is the course taken, according to the authors in question, by the particles of coal that become embedded in the lungs of miners, and produce

what is known in medicine as *anthracosis*. Like pulmonary tuberculosis, pulmonary anthracosis would appear to originate from the digestive tract.

These experiments have been repeated in a number of laboratories, and it must be confessed that the results obtained by the majority of the experimenters were not the same as those of Vansteenberghe and Grysez. This lack of agreement is to be explained by the technical conditions of the experiments; it is not so easy as might be supposed to introduce food and microbes into the digestive tract and *into nothing else*, even though a stomach tube be employed. According to certain authors, owing to the "regurgitating movements" of the alimentary canal, light particles are capable of rising up through the œsophagus into the throat, and of being drawn thence into the trachea and lungs. At the time of feeding there would thus appear to be, simultaneously with ingestion, an involuntary backward suction, imperceptible even to the animal itself. It has even been shown by Uffenheimer[1] that (non-pathogenic) microbes introduced into the rectum of guinea-pigs ascend the alimentary canal as far as the pharynx, and can pass thence into the lungs. According to Kast,[2] the regurgitation of food-particles in the œsophagus is the cause of the deposit that gives rise to "furred tongue." Hence, in experiments, there is a certain confusion between the effects of inhalation and those of ingestion. Experimenters have therefore been careful, before administering food charged with foreign bodies, to obturate or plug the œsophagus; and the food has even been introduced directly into the stomach by means of fistulæ. When these precautions had been taken, it was still difficult to equalize all the other conditions under which the experiments were made—the state of the animals at the moment of ingestion, the division of the emulsions of powders, and the intervals after which the animals were killed for the purpose of making a microscopical examination of their organs. The salient fact in all the published memoirs appears to be that dust is capable of passing through the wall of the intestine and making its way into the adjacent glands, but this fact is far from being

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[1] *Deutsche medizinische Wochenschrift*, November 15, 1906.

[2] *Berliner klinische Wochenschrift*, July 9, 1906.

constant ; it is necessary that the dust be administered in large amounts and for several days in succession. Anthracosis which is of intestinal origin possibly occurs, but it is a trifling matter in comparison with anthracosis due to inhalation ; the greater portion of the particles of coal that become embedded in the lungs of miners are absorbed in breathing.

But even though it should be proved that inert dust very rarely passes through the intestinal mucous membrane, this conclusion could not, without more extensive experiments, be applied to microbes. The microscopic bodies that pass through do not, as a rule, do so by means of their own powers ; they are seized by phagocytes and carried into the glands with the chyle. Leucocytes, however, do not behave towards inert particles in the same way as towards microbes, nor is their action the same with all microbes.

That microbes pass through the wall of the intestine and enter the blood is a fact that was discovered long ago. When horses are bled for the preparation of therapeutic serums, good care is taken not to perform the bleeding during digestion, since, after a meal, the blood always contains microbes that have come from the intestine. Experiments with various microbes made by Calmette, Cantacuzène, and Ciuca have yielded results entirely different from those obtained with inert particles in suspension. Ficker has provided us with series of excellent experiments showing that, in the case of the rabbit, and especially in the young rabbit, *Bacillus prodigiosus* passes through the intestinal wall throughout its length, and that the passage is assisted by conditions, such as prolonged fasting and fatigue, which debilitate the organism. It is true that a fatigued organism is already sickly ; it follows, therefore, that the penetration of microbes is not a normal fact of constant occurrence. It has also been said that the passage is possible only owing to lesions in the alimentary tract—small sores, which are not always visible to the naked eye, but are nevertheless channels of entry. The complexity of the problem and the difficulty of making experiments are clearly indicated by the foregoing statements.

From what takes place in the case of microbes such as *B. prodigiosus* or a *Streptococcus*, we cannot yet infer the capabilities of the tubercle bacillus, which is distinguished from

other microbes by so many peculiarities; it has, however, been proved by all the experiments that have been made, that the tubercle bacillus can pass through the intestinal wall. Cantacuzène, who did not observe the penetration of inert powders, *saw* the bacillus of glanders pass between the cells of the mucous membrane, to make its way into the lymphatics and even the lung; now, the bacillus of glanders in many respects resembles the tubercle bacillus. Uffenheimer, who entirely disbelieves the digestive origin of pulmonary anthracosis, is convinced that the tubercle bacillus traverses the mucous membrane, *without leaving behind it any lesion to mark its passage.*

Bartel and Spieler[1] had guinea-pigs kept by a family, all the members of which were suffering from phthisis; the children played with the little animals, which were fed upon scraps from the table. After various intervals the guinea-pigs were killed, and tubercle bacilli were found in all of them. The bacilli were lodged in the lymphatic glands connected with the different portions of the alimentary canal, from the mouth to the intestine; in the glands of the neck in 58·8 per cent. of the cases; in the glands in the mediastinum (between the lungs) in 52 per cent.; in the glands connected with the intestine (mesenteric glands) in 100 per cent. This experiment confirms the opinion that we have already given as the most probable one: pulmonary tuberculosis arises from bacilli which are distributed through the lung by the pulmonary or "lesser" circulation. The bacilli can reach the right side of the heart and the lungs by several channels: there is the intestinal channel, but there are also the vessels adjacent to the mouth and throat: the tonsils are often considered as ports of entry for various microbes. If the bacillus follows von Behring's route, it also penetrates by the glands of the neck, according to the opinion of numerous experimenters and clinicians, including Borrel and Marfan. The intestine is but one of the ways of access to the pulmonary circulation.

Is tuberculosis contracted by inhalation? Can the bacilli that float in the air that we breathe attack the pulmonary alveoli? According to recent experiments communicated to

[1] *Wiener klinische Wochenschrift*, January 11, 1906.

the Berlin Congress, the recognized *rôle* of ingestion must not cause us to disregard that of inhalation. Küss[1] had great difficulty in rendering guinea-pigs tuberculous by adding bacilli to their food, while he easily produced tuberculosis by causing the animals to breathe the air charged with bacilli by means of a spraying apparatus. Findel,[2] operating *on dogs*, and counting as best he could the number of bacilli administered, produced tuberculosis by the inhalation of about five millions of bacilli, while an ingested dose of some six milliards remained innocuous. According to this experimenter, in order to produce tuberculosis in the guinea-pig by way of the alimentary canal, six million times more microbes would be necessary than by the respiratory channel.

These experiments do not invalidate the results obtained by Calmette and Vallée. Findel admits that he has not experimented upon calves, and, as we know, it is bovine tuberculosis with which von Behring and his adherents are dealing. It is more than probable that the behaviour of a tubercle bacillus is not the same in the intestine of the calf as in that of the dog. Under natural conditions it never happens that we breathe in a few hours air charged with millions of microbes ; we inhale a few such organisms, which are swept up and devoured by phagocytes in the first portion of the respiratory tract. There is even far less chance of our swallowing milliards of microbes in our meals ! The police force of the intestine, however, is liable to be baffled more often than that of the trachea and the large bronchi : the intestine is often chafed by hard bodies, or punctured by worms like *Trichocephalus*, which has been proved to be capable of inoculating the mucous membrane of the appendix with the microbes found in appendicitis, and the wall of the intestine with the microbe of typhoid fever. There is no reason to deny the occurrence of tuberculosis through inhalation, and there is still less reason to deny that the disease is contracted by ingestion : the one origin of the malady does not exclude the other.

Yet the strongest proofs of the penetration of the tubercle bacillus by way of the intestine are not those furnished by

[1] *Bulletin médical*, 1907, No. 14.
[2] *Zeitschrift für Hygiene*, Bd. lvii.

experiments performed under artificial conditions, but rather the autopsies on children mentioned above, in which tuberculous lesions are found in the intestinal glands *alone*, and the bacillus is manifestly of *bovine* origin. These clinical facts are natural experiments, which in the present case are more valuable than those of the laboratory.

Finally, we have not to choose between tuberculosis through inhalation and tuberculosis through ingestion ; both exist, and we cannot acquit either milk or expectoration. Inhaled and swallowed, the dust of streets and carriages where people spit is dangerous. The conclusion to be deduced from all these investigations is, that it is more than ever necessary to reinforce the old ordinances against spitting and dust by the surveillance of slaughter-houses and dairies.

The experiments upon alimentary tuberculosis have suggested a new process of bovovaccination by way of the digestive tract. Instead of a subcutaneous inoculation of vaccine-bacilli, or two inoculations in the veins, Calmette proposes a vaccinating meal, that is to say, a meal to which are added vaccine-bacilli, either normal human bacilli or bacilli modified by various physical or chemical agents ; heat, iodine, hypochlorite of soda, glycerine, or salt solution. In several series of experiments, guinea-pigs have acquired a marked resistance to the virulent test, which also consists in an infecting meal ; heifers and goats have given encouraging results. We cannot help reflecting, however, that bovovaccination according to von Behring's method also gave rise to lively hopes, and it is to be feared that vaccination by way of the digestive tract may likewise merely confer a transitory resistance. The experiments that are in progress will furnish the answer, and they have already established facts which will retain a certain value apart from therapeutic success.

When calves are made to ingest on a single occasion a small dose of tubercle bacilli, the animals are, for two or three months, under the influence of tuberculosis (they react to tuberculin), and they then appear to recover. But if several infecting meals be administered at short intervals, the initial lesions, instead of healing, are aggravated owing to the number of these meals and the quantity of virus ingested on each occasion. It is highly probable that human infants behave in this respect

like calves, and it is for this reason that Calmette adds to the hygienic treatment of tuberculosis this new rule—above all shield the patient from successive reinfections. If we are attacked by tuberculosis, there is a good chance of recovery from the first attack; but if we from time to time absorb bacilli, through the air, expectoration, or milk, these repeated infections, however minute they may be, jeopardize the recovery. A tuberculous subject ought therefore to be shielded from tuberculous contagion no less strictly than one who is healthy.

At the time of the Melun experiment, Vallée and Rossignol recognized the necessity of isolating calves after inoculation with bovovaccine. The period of *hypersensibility* to tuberculosis that follows the treatment and precedes the period of relative immunity, has been referred to by von Behring, and subsequently by Belfanti and Stazzi; and Calmette has confirmed by experiment the danger of successive reinfections. These facts are connected with one another, and bring us to the law that governs the evolution of tuberculous disease, which is that, instead of vaccinating, a first attack produces susceptibility.

The gist of the whole matter is to discover whether this hypersensibility gives place to resistance, and whether such resistance is lasting or transitory. The history of bovovaccination shows that the resistance is precarious and transient, and that finally, after about a year, the animal is more sensible to tuberculosis than ever.

Nevertheless, as is proved by the number of cases of spontaneous recovery that are observed, man possesses means of combating tuberculosis, and it will be necessary to find out how to increase the natural power of resistance of the cells. The calcified tubercles, that is to say tubercles incrusted with lime salts, in which the bacilli finally die among the dead cells, are the result of spontaneous action. It sometimes happens that we find in the cells more or less recognizable remains of bacilli, which are tubercle bacilli in a fossil condition. The way in which Koch's bacillus is digested, and, so to speak, fossilized by the phagocytes of the souslik and the gerbil was described by Metchnikoff quite a long time ago; and the same scientist has also observed that the mites in bee-hives, which feed on wax, have the power of digesting large quantities of

Koch's bacilli. The bacillus is enveloped in a waxy covering, and it is this that the mites attack. This observation, which has been followed up by Metalnikoff, a Russian zoologist, has led to some curious experiments, which display the power of the activities of cells.

Metalnikoff injects human tubercle bacilli into the body of this mite (*Galleria melonella*), and, with the help of histological technique and the microscope, he seeks from time to time to discover what has become of them. He finds that they are enveloped and in process of being digested by the leucocytes, several of which frequently combine in order to engulf a cluster of bacilli; there is then formed an enormous multinuclear phagocyte, which is in every respect similar to the cells discovered more than half a century ago in mammalian tuberculosis and termed *giant-cells.* In a few hours the bacilli are digested; they leave behind them as a residue a brown, amorphous matter, around which the leucocytes form an enclosing capsule, which isolates it from the remainder of the organism; this residue is finally expelled. The mite suffers no ill-effects from the injection, and in due time it becomes a nymph and subsequently an adult; it is endowed with natural immunity.

It is a curious fact that *Galleria*, which so readily digests human and avian tubercle bacilli, does not possess the same power as regards the tubercle bacillus of cold-blooded animals. The bacillus of fishes is pathogenic to it, and kills it in a few days; it allows itself indeed to be engulfed by the phagocytes, but does not, or not so quickly, allow itself to be digested. It intoxicates and kills the cells of the mite, just as our bacillus kills our cells; no isolation capsule is formed around the microbes, and the organism succumbs owing to the exhaustion of its means of defence.

It is indeed the waxy envelope that excites the digestive activity of the phagocytes; in fact, when Metalnikoff injected into a mite a paste which he had prepared from wax extracted from tubercle bacilli, agglutinated with a little gum arabic, the paste was digested like the bacilli. Extracted from the organism, and in a glass tube, it appears that the blood of the mite kills the bacilli and transforms them into corpuscles, which no longer possess the properties due to the waxy envelope, which has disappeared.

We must not expect practical results from these experiments, which, however, are interesting owing to the light that they throw on digestion in phagocytes. The activity of the cells in *Galleria* is due to the presence of a *lipase*, that is to say, a ferment capable of digesting fatty matters; lipase exists, in small quantities, in the blood of various species of animals. We must not, however, be too ready to believe that, even though human leucocytes should secrete in abundance a lipase as active as that of *G. melonella*, man would possess the same immunity to the tubercle bacillus; the microbe does not consist merely of the coat of wax that covers it. There is a highly pathogenic bacillus, that of glanders, which causes the formation of tubercles analogous to those of Koch's bacillus, although it is not enveloped in a coat of acido-resistant wax.

We must be more resolute than ever in putting antituberculous hygiene in force; with method, perseverance, and time tuberculosis among human beings and cattle would be stamped out, but hygiene is everlastingly held in check by prejudice, apathy, and indolence.

Hygiene is understood and practised with conviction only by those in whom the disease has already made its appearance, and by their attendants, who love them and are alarmed; the strong and healthy in no way concern themselves about the rules of hygiene and prophylaxis.

The special efforts already made have touched the public slightly, but have not converted nor made a deep impression upon it. To convert those who are prosperous, rich, and refined is not what we desire; hygiene must enter into the habits of the people at large, and spitting in the streets must be prohibited like every other act of uncleanliness.

People expectorate in the streets almost as much as they used to do; there is less spitting in omnibuses and tramcars, except sometimes by the conductor, who in certain vehicles appears to have reserved the privilege to himself, and the driver, perched high up above regulations; in trains it is better not to enquire what happens. In France all hygiene is powerless against the delightfully easy-going methods so specially characteristic of that country, where "Smoking" and "Non-Smoking" compartments are treated with equal indulgence. The railway companies might at least spare their special labels.

Sputum is indeed the enemy. If fresh proofs of this be required after all those that have been accumulated, some recent experiments by Bartel may once more be quoted ; guinea-pigs which live among phthisical persons become tuberculous but hardly ever do so provided that the patients always take care to use their spittoons.[1] In cages in our laboratories healthy guinea-pigs have been kept with others suffering from tuberculosis, but were never infected by them, since guinea-pigs do not spit. Cattle contaminate each other because they cough (which is equivalent to expectorating minute droplets charged with bacilli) over drinking-troughs and mangers.

At all Congresses, compulsory notification, a necessary condition for disinfection, is regarded as a measure that ought to be enforced. It has been adopted by several nations, but we will have none of it, since it is troublesome. Are we, then, to infer that the disease is not ?

We are waiting for science to supply the cure. We are expecting to receive a remedy that shall be highly convenient, extremely rapid, and thoroughly infallible ; a hypodermic injection, a pill, or even less, which shall purify the system without interfering with either our business or our pleasures. We rely on the State, as the universal provider, to institute, at the smallest possible expense, operations against tuberculosis.

Science can work wonders, but it does not perform miracles ; it utilizes the forces of nature and teaches us to direct them. It has already taught us sufficient to enable us to cure tuberculosis by stamping it out ; we, however, are *unwilling* to take the necessary steps, or our willingness is but half-hearted. If only the people at large were of one mind on the matter, it would be seen that the power of hygiene is sufficient to transform human life.

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[1] *Wiener klinische Wochenschrift*, September, 1907.

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TETANUS.

Not very long ago, I again saw a man dying of tetanus in a Paris hospital. There was no isolation ward, so the bed had been screened off in a corner, in order, by means of partial darkness and quiet, to lessen the painful irritability of the patient. Between white curtains lay a tall and handsome young man of fine physique; his jaws were locked, his eyes fixed, and the neck and back rigid. He could hardly speak, and had difficulty in drinking; water coming into contact with the throat caused a spasm of suffocation. On the right hand there was a dressing covering a wound. Except for the comatose condition produced by the administration of powerful doses of chloral, the unhappy man would have retained consciousness until the end. The pulse was rapid and there was fever; death ensued on the following morning. The injury to the right hand was a gunshot wound received twelve days previously, while handling a firearm, and the mangled flesh was encrusted with dust or earth. A week later the man felt stiffness in the muscles of his jaws, and in four days from this the disease had done its work.

Tetanus, then, which is a complication of a wound, arises in this way. It is known as surgical or traumatic tetanus, the "painful spasm" (*spasme par douleur*) of Ambroise Paré, "convulsion" of Guy de Chauliac, or again, on account of the first symptom, *trismus* or lockjaw. It supervenes after contusions, wounds due to crushing, deep punctures, or compound and exposed fractures, and especially when the injured tissues have been soiled with earth, dirt, or manure. It is prevalent on battlefields, where it carries off the wounded, both men and horses, in hundreds.[1] The smallest wounds may be dangerous,

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[1] Military statistics show that the average is 1 case of tetanus per 300 wounded. Examples: Crimean War, 1 per 465 (British Army), 1 per 332 (French Army); Franco-Sardinian hospitals in 1859, 1 per 143; Prussian Army

and it has been proved by many an example that human lives depend upon trifles : a fish-bone fixed in the throat (Larrey), foreign bodies in the eye or ear, the extraction of a tooth, or the excision of a corn ; a scratch on the nose with a dirty finger-nail ; a snake-bite, or a blister ; a vaccine ; a prick from a needle, or from a thorn in plucking a rose ; a sting from a bee ; a prick from a syringe in the case of morphiomaniacs. Whether from accidents, wounds, or surgical operations, there was always danger of tetanus before the epoch of asepsis.

Puerperal tetanus and *tetanus neonatorum* are varieties of traumatic tetanus. In a woman after childbirth there are raw surfaces which it is necessary to protect from all contamination ; tetanus after confinement has fortunately become as rare as after operations, but tetanus in new-born infants is extremely common in hot countries, and is a scourge in French West Africa. In Guiana, according to Bajon's memoirs (about 1760 to 1770), following ligature of the umbilical cord, scarcely a third of the children escaped, and in Jamaica quite a quarter of the infants born died of the disease ; at the close of the eighteenth century there was much mortality from it among children in the Vivarais district, in the South of France, where the disease was called *sarrette*. Bajon states that the Indians in Guiana applied a plaster to the umbilicus after cutting the cord, and that, in consequence of this practice, they lost few children. One would like to know the ingredients of this plaster, since in St. Hilda Island, in the New Hebrides, at the present day, many children die from tetanus because earth is mixed with a similar plaster.

At Saigon, in Cochin China, on the admission of the native midwives, or *bâ-mu*, 30 per cent. of the new-born infants died, only three years ago, from umbilical tetanus (40 per cent. at Cholon, according to the estimate of the municipal authorities at the time of the foundation of the lying-in-hospital). It was in order to combat umbilical tetanus, among other scourges, that Dr. Dejean de la Bâtie instituted, in 1905, his system for

in 1864, 1 per 140; Siege of Strassburg in 1870, besieged 1 per 185, besiegers 1 per 116; German Army in 1870, Versailles hospital, 1 per 100. In the War of Secession there were 116 cases of tetanus in 30,000 amputations, and 374 cases among 212,000 wounded.

the supervision of births among natives. Instruction in hygiene is given to the *bâ-mu*, they are provided gratuitously with aseptic and antiseptic dressings, and, in order to encourage them, a premium of one piastre is awarded to them for each infant that survives until the eleventh day without any complication arising, after having been treated in the prescribed manner; during these eleven days the baby is visited thrice. The mortality from tetanus has fallen from 30 per cent. to 6 per cent. (in 1907 there were 14 deaths from the disease in 526 births during the period from March to July;—notes by Dr. Montel).[1]

Horses, cattle, and sheep are liable to tetanus, and the disease in horses has always given much trouble to army veterinary surgeons. In a horse suffering from tetanus there is lockjaw, great difficulty in swallowing, and stiffness of the muscles of the neck; when *contraction* extends to the muscles of the body, the horse carries his head high, with the muzzle thrown up like a stag, in consequence of which tetanus in the horse was termed by the old veterinary surgeons "stag sickness" ("*mal de cerf*"); the tail sticks straight out, and the stiffened limbs look awkward; the animal presents the ridiculous appearance of a wooden horse. Seventy-five per cent. of horses attacked by tetanus succumb.

It sometimes happens that tetanus occurs without the smallest wound, or anything in the shape of a *port of entry* being discoverable on the closest examination; this is the so-called spontaneous or medical tetanus, as opposed to surgical or traumatic tetanus. In former days tetanus of this kind was attributed either to the action of cold, and especially damp cold—as in the case of a man drenched by a downpour of rain while sweating, or a bather seized with a fit of shivering on leaving the water—or to the action of excessive heat. The frequency of tetanus in the Antilles or Guiana appeared to the older writers to be connected with sudden oscillations in the temperature.

Between an injury and the first symptoms, there *always*

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[1] Dr. R. Montel, *La Surveillance de la Natalité indigène et la Prophylaxie du Tétanos ombilical à Saigon*; a Report presented to the Colonial Council, Saigon, 1906.

elapses a period of incubation of from four to twelve days, seldom more, and seldom less. A few years ago Dr. Nicolas, of Lyons, had a severe though not fatal attack of tetanus, exactly four days after pricking his finger with the point of a needle dipped in tetanic toxin. In the case of both human beings and horses, whatever be the seat of the initial injury, the first symptom is the contraction of the muscles of the jaws; a patient telephones for his medical attendant, and can scarcely articulate. When the muscles of the trunk are affected, the body is bent in the arc of a circle, the direction of which depends upon the situation of the wound. The contractions take place in spasms, with remissions and exacerbations; a slight stimulus, a current of air, a movement of the bed-clothes,[1] or the touch of the finger in taking the pulse, produces paroxysms, as in hydrophobia. Death usually occurs from asphyxia or in an attack of syncope, three or four days after the first symptom, in acute cases. When the disease develops slowly, recovery is possible—in from 10 to 30 per cent. of the cases, so far as figures can be given—but the patient may suffer for months from stiffness and heaviness of the limbs.

Tetanus which follows a wound in the face sets in after a very short period of incubation; it is marked by violent spasms of the throat, and is the form of the disease described by Rose as hydrophobic tetanus; the incubatory period is longer, from a fortnight to twenty days, in the case of tetanus which originates in the internal organs; death supervenes rapidly, in terrible paroxysms of suffocation. Many a medical man has been a helpless witness of such excruciating sufferings on the part of patients, who retain their intelligence and physical and mental sensibility until the last moment.

Pre-Pasteurian ideas on the subject of tetanus were of so chaotic a character, that there would be little difficulty in forming a collection of theories which would appear absurd at

[1] "I have seen a patient in whom the rustle of a silk dress was sufficient to produce these attacks (or paroxysms). I have seen others in whom the same effect was produced by moving a candlestick along a marble chimney-piece. In 1830 I saw tetanus produced in the wounded, and made cruelly severe, by the discharge of musket-shots and fireworks outside the hospital in the rejoicings after victory; and above all I have known it occasioned in its acutest form by the ringing of the alarm-bell" (Dupuytren).

the present day; it is fairer to select from the writings of the older authorities such observations as must have served to guide experimental research. In the opinion of Ambroise Paré, tetanus arises not only from wounds, but also from dirty dressings; it is evident that the disease is one which affects the nervous system, and Boerhave compares it to hydrophobia; Rose describes the hydrophobic form; in the time of Broussais we find frequent reference to irritation of the spinal cord.

More is to be learnt by observing the conditions under which the disease occurs, and it will naturally be asked whether tetanus does not come from the soil. Bilguer remarks that it is more common among wounded men who are left on the field for the night; in 1870, before Metz, while tetanus was rare in the hospitals in the town, there were so many cases in the Saulcy field-hospital, which was pitched on a damp and low-lying spot, that it had to be evacuated. In 1859, according to Demme, tetanus was more common among the Austrian wounded, who were left on the battlefield for a longer time, than among those belonging to the victorious army. Wounds soiled with earth are the most dangerous; there are gardens and fields that are infected with tetanus, and gardeners and grooms are among those who are most frequently attacked.

The idea suggested by the observations of military surgeons, and the influence of the soil and earth, is that the disease might well be epidemic. It was noted by Billroth that there were years in which tetanus was rife, and others in which it did not occur; in surgical practice isolated cases have scarcely been met with—the cases occurred in groups. At Rouen, Dr. M. Nicolle saw eight fatal cases in a small ward of a dozen beds, and B. Anger saw four cases in patients occupying adjacent beds, in quite a small ward. Some twenty years ago near Achères, not far from Paris, cases occurred one after the other, in both human beings and horses.

At a time when there was no idea of a microbe, it was reasonable to suspect the atmosphere as well as the soil, and variations in temperature appeared to be more dangerous than constantly low or constantly high temperatures.

Larrey states that, in the Austrian campaign of 1809, the wounded who happened to be most exposed to the effects of the cold and damp air of the freezing nights in spring, after

having endured different degrees of very high temperature during the day, were almost all attacked by this disease, which was prevalent only at this season, when the thermometer fell nearly every night to half its daily maximum. The day on which the battle of Bautzen was fought was very hot, and the following night very cold ; next day there were 110 cases of tetanus. "I have also observed," writes Larrey, "that, although the essential cause may always be pretty much the same, this complication does not usually make its appearance among the wounded except at the seasons when the temperature passes from one extreme to the other." After Austerlitz and Eylau, and during the retreat from Russia, there was scarcely a case of tetanus ; the temperature was very low, but uniform. It was the same in 1870, at Belfort, with the Army of the Loire and the army of the East. Sédillot says : "Our wounded at Constantine in 1836, who were placed in rooms without doors or windows, and in narrow corridors, and had to endure hot days and frosty nights, were attacked by tetanus in very large numbers."

Heat and heat apoplexy do not cause, but are conducive to tetanus. Vincent, of Val de Grâce, quotes some curious cases, old as well as recent, of which he, not long ago, gave the experimental explanation :—

In hot countries, says Burot, tetanus assumes an almost foudroyant form, since it is usually fatal in less than twenty-four hours. In Spain, according to Fournier-Pescay, on several occasions, after having marched all day under a blazing sun, over burning soil, a number of our men were attacked on the following day by *universal* (generalized) tetanus. In a case published by J. More, in the *Lancet* of September 16, 1876, a farm-labourer, who had been working in the fields during intense heat in the month of July, was subsequently prostrated by severe indisposition. A few days afterwards he showed the first symptoms of tetanus, which proved fatal ; there was no wound nor even a scratch on the body. In the case of a soldier who came under his observation suffering from tetanus, Vincent failed to discover any predisposing cause other than a heat-stroke ; six or seven days prior to the onset, the man had done a march under a scorching sun.

The first experiments upon tetanus date back some fifty

years. Surgeons who, since the time of Ambroise Paré, were in dread of tetanus supervening in the case of badly-closed, ill-dressed, and suppurating wounds, were led to believe that there was formed in the wounds a poison, which spread through the blood and affected the nerves. The ptomaïnes, that arise in the course of the decomposition of animal tissues, furnished an example of poisons capable of producing spasms. Vulpian thought that, by injecting putrid matter into the circulation, he could obtain an exaggeration of the reflex phenomena, not without analogy to certain symptoms of tetanus.

In the case of an animal sensible to tetanus, the disease was never produced so long as some external agent was not added to lesions created in the organism. Each time that the operation was performed aseptically, it was of no use to pinch, twist, crush, or ligature muscles and nerves, to imitate the work of swords, bullets, shell-splinters and surgeons, to stimulate the nerves or excite them to exaggerated reactions, as in the case of experiments made upon decapitated frogs; the result in each case was *nil*. On one single occasion, Brown-Séquard succeeded in inducing tetanus by driving a nail into the paw of a dog; perhaps, however, the nail had carried something in with it.

After the first conquests of bacteriology, it was thought that tetanus might be an infectious disease, and its experimental transmission was attempted according to the approved method in the case of other infectious disorders. In 1869, Arloing and Tripier injected into the blood-vessels of rabbits and dogs blood and pus taken from corpses of wounded men who had died of tetanus; they also injected intravenously into a healthy horse 200 c.cm. of blood from a horse suffering from tetanus; in neither case was there any result.

A dog can be infected with rabies by injecting part of the brain of a rabid dog, but Nocard, who tried the experiment with nerve-tissue from a tetanic horse, failed to produce tetanus.

Some experiments fail to succeed, although well performed; when we launch forth into the unknown we need good luck as well as ingenuity. About 1882 began the era of successful and fruitful experiments, and from this moment the story of the investigations upon tetanus is a wonderfully instructive chapter in experimental medicine.

In the year 1884 two Italian doctors had in their service a young man who died of tetanus; he had on his neck a small pimple, which he had scratched with his nails, which were no doubt dirty. The pimple was excised and crushed up in a little water, and the liquid, on being examined under the microscope, was found to contain microbes of various kinds. When twelve rabbits were inoculated with it, eleven of them developed tetanus; from these rabbits others were inoculated, and in this way the *passage* was successfully performed twice in succession. Thus it was proved that tetanus is an infectious and inoculable disorder; the microbe had been inoculated without recognizing it (experiments by Carle and Rattone).

In the same year a young scientist of Göttingen University, who was studying the microbes of the soil, inserted particles of garden mould beneath the skins of rabbits, guinea-pigs, and mice; twelve out of eighteen samples of earth produced fatal tetanus. A little pus taken from an inoculation wound and introduced into other animals caused the latter to become infected; earth heated to 180° C. (356° F.) ceases to be dangerous. By aid of the microscope there was discovered in the earth and in the pus a microbe shaped like a little rod, a bacillus swollen at one extremity, which was called the "pin-shaped bacillus"; this was the microbe of tetanus (Nicolaier's experiments).

In the usual culture media, in contact with the air, the pin-shaped bacillus refused to grow; plenty of microbes developed, but these belonged to other species. Among these other colonies a few pin-shaped bacilli were still found, and the whole, on being reinoculated, again produced tetanus; these, however, were impure colonies, and the pathogenic power of a microbe is proved only by the inoculation of pure cultures.

In 1886, all these experiments were successfully repeated by Rosenbach, who considers that the swelling at one extremity of the bacillus—the head of the pin—is nothing else than the *spore* (otherwise known as the seed) or resistant and germinative form of the microbe. The spore of the bacillus of anthrax, to which Koch and Pasteur had ascribed the occurrence of epizootics of the latter disease, was already known.

A French veterinary surgeon decided to dispense with an instrument which he had been employing in the castration of

horses, because all the horses upon which he had used it died of tetanus. He took the instrument to Nocard, who cut from the surface of the wooden handle a small splinter, which he inserted under the skin of a guinea-pig ; the animal developed fatal tetanus, and the same splinter, when thrust in turn into the skins of a series of guinea-pigs, caused them to die of tetanus one after the other. Vaillard successfully performed the same experiments with minute fragments of the finger-nail of a man who had died of tetanus after having one of his fingers crushed. Nicolaier's pin-shaped bacillus was found by both the scientists last mentioned.

The great merit of making pure cultures of the bacillus is due to a Japanese investigator, named Kitasato. The bacillus of tetanus does not grow when exposed to the air, but only when oxygen does not come into contact with it ; it therefore belongs to the class of anaerobic microbes, the discovery of which was one of the most striking instances of Pasteur's intuition.

The bacillus of tetanus, then, lives in the soil ; it exists in the earth of all gardens, where it is preserved indefinitely in the form of spores, which are the seeds of the microbe. The life of a microbe may be short ; air, light, and the cells of an organism into which it is introduced, shrivel it up, impair its vigour, and kill it. The vitality of the cholera vibrio and of the bacillus of plague is somewhat feeble, so that these organisms are readily destroyed by disinfectants. Other more privileged micro-organisms, when subject to harmful influences, when their vitality is menaced and they no longer find the nutriment necessary to their existence as parasites, are capable of protecting themselves from destruction. They contract a portion of their substance, gathering it together into a minute ball, which surrounds itself with a stout protecting membrane ; this ball of living, though dried and condensed matter, is the spore, which survives when the remainder of the body of the microbe perishes. The spore of the bacillus of tetanus resists ebullition for five minutes ; in a dry condition it withstands a temperature of 110° C. (230° F.) for quite a quarter of an hour ; when in a wound, it defies washing or superficial disinfection, by which ordinary microbes would be destroyed. The reason that Nocard's splinter and Vaillard's fragment of finger-nail

were so virulent was that they were the carriers of tetanus spores ; Eiselsberg, having kept a splinter that had caused a case of tetanus, found that it communicated the disease after two and a half years, and a case is on record in which splinters were still pathogenic after the lapse of eleven years.

It is usually by means of particles of earth that the bacillus of tetanus gains access to a wound, and consequently there is no longer any mystery in connection with the "epidemics" of tetanus on battlefields. The bacillus and its spore do not merely, like a grain of sand, lead a passive and inert existence in the soil, but, under natural conditions, they pass through a regular life-cycle. From the soil, the microbe passes into the alimentary canal of cattle and horses, where, like so many other anaerobic microbes of the intestine, it multiplies abundantly. Passing out with the droppings, it returns to the manure-heap, the field, or the garden ; it takes up its abode in stable floors, in the dirt adhering to boots and horseshoes, on mangers, and on harness ; there is good reason for the remark that it is chiefly owing to the horse that man is attacked by tetanus. The bacillus is revivified by its passages through living beings ; stages of vegetative bacilli alternate with stages of spores, in which life is latent, and these active and reproductive lives, intercalated between the dormant phases, regenerate the microbes and ensure the immortality of the race. Thus it is that the bacillus of tetanus exists everywhere around us in the world of nature.

At the time of the discovery of the tetanus bacillus, microbic diseases were regarded as *infections* in which the microbes swarm in the blood and among the corpuscles. The number of anthrax or plague bacilli found in the body of a sheep or of a man dead of one or other of these diseases is beyond all belief. A few bacilli taken from these milliards of milliards are sufficient to inoculate another subject with the same disease, and so on indefinitely ; but it was shown by experiment that it was not so in the case of tetanus.

One five-hundredth part of a cubic centimetre—or even less —of a pure culture of Nicolaier's bacillus, inoculated beneath the skin or in the muscle of a guinea-pig, is sufficient to produce, after a period of incubation of from twelve to twenty hours, an attack of tetanus which is fatal in thirty-six to forty

hours. When, however, an autopsy is made, and the animal's tissues and humours are examined under the microscope, not a single microbe is found. Even at the point of inoculation, we should have to seek a long time in order to discover a few of these organisms ; the bacillus of tetanus, therefore, does not multiply in an animal which succumbs to the disease.

Not only do the bacilli not multiply, but they become more and more rare, and finally disappear. Pus taken from a tetanic wound will infect a second subject with tetanus, and the wound in the latter subject will yield matter which will communicate the disease to a third. It is, however, scarcely possible to go further ; the *passages* cease as though the virus becomes used up, which indeed it does as regards its amount. If a guinea-pig be inoculated with exactly the dose of tetanic culture necessary and sufficient to kill it, there will not subsequently be found, even at the point of inoculation, material enough to communicate the disease to a second animal ; we are far from being able to achieve the indefinite series of passages so readily accomplished when dealing with other infectious maladies.

This, however, is not all. A trace of pure culture, which has been kept for a certain number of days in the stove, at a temperature of 37° C. (98 6° F.) is fatal to the guinea-pig ; but if we inoculate a stronger dose ($\frac{1}{2}$ c.c.) of a younger culture (three days old) developed at a lower temperature, we fail to produce a fatal attack of tetanus, in spite of the fact that the dose used is very rich in bacilli. This is so remarkable that we might even be led to doubt the specific action of the bacillus (experiments by Vaillard and Vincent).

Another experiment by Vaillard and Vincent is as follows : two of these non-fatal doses are taken, one of which is inoculated just as it is and does not produce tetanus ; the other dose is steeped for twenty-four hours in a small quantity of *aqua chloroformi* : the inoculation of this liquid, *deprived of tetanus bacilli*, produces tetanus ; the cultures, therefore, contain a pathogenic or tetanigenic element, other than the microbes.

The riddle to be solved was cleverly suggested by another interesting experiment. Several mice are inoculated in the tip of the tail with a pure culture, and then all of them have their tails amputated, but at different intervals after the inoculation,

—half an hour, one hour, two, three, and four hours. The only mouse to survive is the one whose tail was cut off in half an hour ; the others all die of tetanus, and in none of them is the slightest trace of a tetanus bacillus to be found (Kitasato's experiment).

It is, therefore, not the bacillus that kills the mice, but a substance produced by it either in the tissues or in the broths in which the culture was made, and this substance spreads through the body so quickly as to kill the animal in spite of the amputation of its tail. It acts like a poison and is the tetanic toxin.

A guinea-pig is not killed with even a strong dose of a culture which is too young, and has been obtained at a temperature below a certain point, because such a culture does not yet contain the toxin, or does not contain enough of it. The same culture is, however, fatal to the animal after having been steeped in *aqua chloroformi*, because by this process the toxin is extracted from the bacilli. Tetanus is not an infectious but a toxic disease.

At the time when these facts were established the idea of a toxic disease was not new, and people's minds were quite prepared to accept it. In 1889 Roux and Yersin had published their studies on the toxin of diphtheria, the bacillus of which disease does not invade the organism, but produces its fatal effect by means of the poison secreted by it. The latter is not a poison of the same kind as morphia, strychnine, and other alkaloids, since its properties cause it to be included among the ferments or *diastases*, which are substances that play an immense part in nature, and are still imperfectly understood. The diphtheritic poison is such that an imponderable trace of it is sufficient to produce effects out of proportion to the dose itself, and Roux's discovery was one of the most striking proofs of the fundamental concept underlying Pasteurian science, which is that microbic diseases are fermentations taking place in the animal body, and produced by specific microbes.

In order to discover the tetanic toxin, it was only necessary to repeat the experiments of Roux and Yersin upon the diphtheria bacillus, and this was done so long ago as 1890. A culture liquid, filtered through a porcelain candle and deprived of microbes, produces typical tetanus in animals (Knud Faber's

experiment). The method of making cultures was perfected, and investigators learnt how to prepare broths of increasing toxicity, and toxins of ever greater strength (experiments by Tizzoni and Mdlle. Cattani, Brieger, Fränkel, Vaillard and Vincent, and others). It is impossible to understand tetanus except by gaining an idea of the fearful power of the tetanic toxin ; a hundred-thousandth of a cubic centimetre of broth (a culture twenty days old) produces fatal tetanus in the mouse ; and a thousandth of a cubic centimetre kills a guinea-pig weighing 500 grammes in sixty hours.

"The quantity of toxin contained in so infinitesimal a fraction of filtered liquid is difficult to grasp ; perhaps, however, the following figures will give an approximate idea of it. A cubic centimetre of this most powerful liquid, evaporated *in vacuo*, yields a dry residue of 0·040 gramme ; when subjected to calcination this residue undergoes a loss of 0·025 gramme, representing the weight of the organic matter. Assuming that these 25 milligrammes belong entirely to the toxin itself, it appears that this weight of organic matter would enable us to kill at least 1,000 guinea-pigs, or 100,000 mice ; the lethal dose would therefore be 0·000,025 gramme for a guinea-pig, and 0·000,000,025 gramme for a mouse. It is scarcely necessary to observe that a very large proportion of the 25 milligrammes of organic matter would consist of substances unconnected with the tetanic poison. How minute then, if indeed ponderable, must be the true dose of toxin capable of causing death! Figures such as these will at least serve to show in its true light the incredible toxicity of the poisons produced by the microbes in artificial culture media, a toxicity *probably inferior to that of the substances elaborated by them in the diseased organism*."[1]

Toxins have been obtained of which a millionth of a cubic centimetre is fatal to the mouse, and Knorr has prepared from the toxin a dry precipitate, one gramme of which would kill 150,000,000 mice. By taking into account the weight of animals upon which experiments have been made, and stating the minimal quantity lethal to one gramme of each animal, species can be classified in order of sensibility. The horse is

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[1] Vaillard and Vincent, "Contribution à l'étude du tétanos," *Annales de l'Institut Pasteur*, 1891.

the most sensible : if we express by the figure 1 the quantity lethal to a given weight of horse, the quantity that kills the same weight is 2 in the case of the guinea-pig ; 4 in that of the dog ; 13 in that of the mouse ; 2,000 in that of the rabbit; and 200,000 in that of the fowl ; that is to say that the fowl is 200,000 times more resistant to tetanus than the horse. Needless to remark, human beings have not been inoculated in order to gauge their sensibility, but it is certain that man is highly sensible to the tetanic toxin.

These comparative experiments are still more interesting when extended to the whole of the animal kingdom. Metchnikoff has observed that insects and their larvæ are insensible to the toxin of tetanus ; scorpions are also insensible, and so are the axolotl and the frog when kept at a low temperature, but when the temperature of the medium in which they are placed is raised to 30° C. (86° F.), and over, they become sensible. Alligators and tortoises are insensible whether hot or cold ; when injected in enormous doses into the tortoise, the toxin is retained for months in the blood without losing its activity. The tortoise is therefore capable of serving as a living bottle in which to preserve the toxin, which keeps much better in it than in a phial, unless great care be taken to protect the latter from the action of heat and light. Sensibility to tetanic toxin is therefore a special attribute of warm-blooded animals.

With the toxin alone, and without tetanus bacilli, all the phenomena of tetanic disease can be reproduced experimentally—a noteworthy lesson in physiology and toxicology.

Although the toxin does not produce any lesion at the point of inoculation, it is here that the disease commences. Local at the outset, the malady subsequently extends to the rest of the body ; the symptoms, and the manner of reacting and dying, vary according to the regions and the organs inoculated ; the toxin plays upon the organism like a musician upon a clavier.

If a guinea-pig be inoculated in the hind leg with the toxin, after the lapse of time necessary for incubation the limb becomes stiff ; the affection then extends to the corresponding leg on the other side, manifests itself next in the muscles of the back, then (more slightly) in the front legs, and finally in the neck and head. The guinea-pig dies in a state of complete rigidity and with a raised temperature, the symptoms exhibited

being precisely the same as those of surgical or traumatic tetanus in man consequent upon a wound in the finger or foot, except that in man, and also in the horse, but in no other animal, whatever be the seat of the injury, the disease commences with stiffness of the jaws.

Tetanus resulting from inoculation in an internal organ, such as the lung, liver, or peritoneum, is very rapid in development ; in this case there is no permanent stiffness of the muscles of the limbs, but the animal gasps for breath with convulsive yawns and hiccoughs, has spasms at intervals, and death is accompanied by a marked feeling of coldness to the touch. When the inoculation is made in a vein, tetanus sets in with generalized contraction : the disease resulting from direct inoculation in the brain bears no resemblance to surgical tetanus, but is a kind of psychic delirium, with fits of convulsions which resemble attacks of epilepsy, hallucinations, and grinding of the teeth, while at times the animal dashes away in alarm. " During the attack the animal appears to act in response to an internal impulse, and, in thinking over the matter, we are led to wonder whether many mental disorders are not also the result of certain nerve cells becoming affected by microbic toxins, elaborated at a given moment in the intestine or in some other part of the body " (Experiments on cerebral tetanus by Roux and Borrel)[1].

The scientist in the laboratory improves upon Nature, which does not act spontaneously in *all* of these ways ; but it is by these experiments that we are enabled to account for the strange facts that were formerly inexplicable. When tetanus in man supervenes upon an injury to the face, it commences with contractions confined to the parts controlled by the facial nerve : median paralysis if the wound be at the tip of the nose ; paralysis on the right or left, according as the injury is on the one side or the other. Certain terrible and rapid forms of tetanus, without stiffness of the limbs, but with spasms of suffocation, are to be explained in the same way as visceral tetanus in the guinea-pig, the toxin having attacked the area of the great sympathetic system. If the poison comes in

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[1] After his work on rabies, Pasteur thought of making experiments upon epilepsy

contact with nerves and paralyses muscles (respiratory muscles, diaphragm, and larynx), the action of which is indispensable for the maintenance of life, the organism, having a vital part of its system deranged, is doomed to death, while the same dose of toxin, inoculated in the foot, would merely have produced a non-fatal attack of tetanus.

The toxin secreted by tetanic bacilli in a wound acts upon the nerve fibres of the injured part, and travels along the nerves to the spinal cord and brain ; it is possible to intercept it on the way, and to determine the direction in which it is extending. In the case of a guinea-pig inoculated in the foot, the main path that conducts the toxin from the foot to the brain is constituted by the sciatic nerve ; by removing this nerve and reinoculating it into a healthy animal, which either contracts tetanus or not as the case may be, it can be shown that one hour after the first inoculation the sciatic nerve contains toxin, and that when three hours have elapsed it does so no longer. The toxin travels from the periphery towards the centres, from below upwards, and not in the contrary direction ; it extends with equal readiness along the three kinds of nerve fibres, sensory, motor, and sympathetic (experiments by Morax and A. Marie, Meyer, and Ransom). It is also certain that part of the toxin inoculated passes into the blood, and so goes to bathe the nerve fibrils which extend over the entire surface of the body. When a sufficiently strong dose of toxin is injected into the veins, the resultant attack of tetanus is characterized by generalized contractions.

Doubt has, however, been cast upon this mode of absorption of tetanic toxin by recent experiments by V. Henri and Mdlle. Cernovodeannu. According to these authors, the toxin is distributed by the blood and lymph, and absorption by the nerves, even if it occurs, cannot produce tetanus by itself alone.

The larger the nervous surface affected, the more severe is the effect of a given dose of toxin. If, for example, a guinea-pig be killed by injecting into it at one point a thousandth of a cubic centimetre of toxin, one-tenth of this dose will be fatal if inoculated simultaneously at several different points.

The bacillus of tetanus is everywhere, and, as we have seen, its action is due to a toxin of terrible power. Every day, in the world of work and sport, in the factory, garden, or the

stable, in touring, cycling, and motoring, injuries of various kinds, falls, and bruises are met with. Why is it then that tetanus, which might be expected to be of daily occurrence, is fortunately so rare ; how is it contracted, and how can it be avoided ? This the problem of the *etiology*, properly so-called, of tetanus, the solution of which has been furnished by the experiments of Vaillard, Vincent, and Rouget.

The seeds or spores of tetanus bacilli derived from a culture broth are impregnated with toxin, but those that are produced under natural conditions and enter a wound are devoid of it ; the reader should note this distinction between spores charged with toxin and those without toxin, which are known as *pure spores*.

In order that tetanus should supervene upon a wound, it is necessary that the pure spores contained in it germinate and produce bacilli, and that the latter secrete in the tissues the lethal toxin. The patient contracts tetanus if the spores germinate, but not otherwise.

The spores in the wound would always germinate did they not meet with those enemies of the microbe and protectors of the body, the white blood corpuscles, the phagocytes of Metchnikoff, which are capable of seizing and digesting them. The spores germinate if they escape the phagocytes, but are destroyed if the latter do not miss them ; the etiology of tetanus is a matter of phagocytosis.

The spores charged with toxin from culture flasks can, by destroying the toxin, be transformed into "pure" spores, and it is with these pure spores that experiments must be made in order to reproduce in the laboratory the conditions realized in Nature.

The toxin can be removed from the spores either by heating them at a temperature of 75° C. (167° F.), or by washing them for hours under a stream of water. I inoculate a guinea-pig subcutaneously with half a cubic centimetre of pulp composed of these pure spores, and the animal receives millions of them, yet tetanus does not result. When we reflect that a prick from a splinter can cause the disease, we know not what to say to this paradox, for what has become of these millions of spores ?

To continue the experiment : by raising the skin of the inoculated part and scraping the exposed tissue with the point

of a scalpel, I collect a whitish substance of a pulpy consistency, which I smear on a slip of glass, stain by a suitable method, and examine under the microscope. The pulpy substance is composed of a mass of white corpuscles, or phagocytes, crammed with spores, of which each phagocyte contains from ten to thirty, resembling a bagful of balls. Three days after the injection there is not a single spore that remains free and has not been seized by a phagocyte. The spores are not merely devoured, but are digested by the phagocytes, and disappear like the food that we eat. At the end of a week none of them are any longer to be found. . . . Yet stay : here and there, in some dyspeptic phagocyte which has not accomplished its function, one or two spores, more difficult to digest, perhaps remain ; and it may be that these troublesome survivors will be met with again.

So much for the guinea-pig. But since this animal, which is highly susceptible, defends itself by phagocytosis so triumphantly against the millions of spores injected into it, how is it that a man, in spite of his phagocytes, develops tetanus through half a dozen spores which may have slipped into a wound? The reason must be that in wounds that lead to tetanus the phagocytes are rendered incapable of action.

Instead of two millions of pure spores, I next inject into a guinea-pig a dose a thousand times smaller, but I endeavour to protect these spores against the vigilant voracity of the phagocytes. Means for doing so exist; there are substances, such as lactic acid and trimethylamine, which are repugnant to phagocytes and put them to flight. If, with the spores, I inject a small quantity of lactic acid, the phagocytes are driven off, the spores germinate, and the guinea-pig develops tetanus. Instead of putting the phagocytes to flight I can distract them, occupy them with something else, beguile their appetite with another bait; I shall not introduce lactic acid, since I might be met with the objection that this acid produces some effect upon the germination of the spores which I have not taken into account. Simultaneously with the inoculation of the spores, I inject into the blood fine particles of carbon ; the phagocytes play their part as police, fill themselves with the powder, on the arrival of the spores are incapable of further action, and tetanus inevitably ensues. I can obtain the same result without an

accessory injection, if I preserve the spores by wrapping them in sterile paper ; by an aseptic operation, needless to remark, I insert this packet of spores beneath the skin of the guinea-pig and await the result. The paper is not an insuperable obstacle to the phagocytes ; they pass through it, though with difficulty and in very small numbers at a time, so that they do not arrive in sufficient strength to make a rapid clearance. If the paper be thin and permeable it will still be possible for a slight and tardy attack of tetanus to set in ; if the paper be thicker the spores that are not devoured will have time to germinate and give rise to tetanus of the normal type.

In order, then, that a wound may lead to tetanus there must be something more than a mere introduction of spores into living tissue ; the accessory conditions are supplied by foreign bodies, associated microbes, and malnutrition of the torn and bruised tissues. Experiments will show the efficacy of these factors.

Making an incision in the skin and muscle of a guinea-pig with an aseptic bistoury, I raise a flap of skin or muscle in the orthodox manner, and introduce pure spores into the wound : result, no tetanus. I insert pure spores into lesions such as a burn, which mortifies skin and muscle ; a pinch or a bruise, with extravasation of blood ; a compound fracture of the bones of a foot : result, tetanus. Now I understand the danger of an injury to the knee, resulting from a fall on a loose and stony road, of a lacerated gunshot wound, or of a burn or frost-bite on one of the extremities.

Affixing tetanus spores to a fragment of flint, a splinter, and grains of sand, I introduce these foreign bodies into wounds. If the wound be aseptic, and if it be closed aseptically, it is rare for tetanus to develop ; but if the wound heal badly—which it is liable to do owing to the uncleanly condition of the foreign bodies—if it become infected and suppurate, tetanus always supervenes.

The microbes that enter a wound in earth and dust occupy the attention of the phagocytes, and play the part of the particles of carbon that we injected together with the spores. Moreover, by a dangerous interaction, they may favour the culture of the tetanus bacilli, just as in the field one plant promotes the growth of another. Thus the disease that would not

be caused by a microbe alone, is produced by an *association of microbes*, a phenomenon of very general occurrence in the etiology of infectious diseases. Let us suppose that a particle of earth, inoculated just as it is, causes tetanus ; a particle of the same earth, heated to 80° C. (176° F.), is innocuous ; the heating process did not kill the tetanus spores, but only the associated and auxiliary microbes. If, to the particle thus purified, we restore some of the microbes destroyed by the heating, it again becomes capable of producing tetanus. With pus from a tetanic wound, the same experiments can be performed as with the earth ; in its natural state it causes tetanus ; when heated it does not ; if some of the associated microbes, derived from pure cultures in tubes, be restored to it, the pus once more becomes tetanigenic.

It is not necessary that *all* the conditions enumerated above —foreign bodies, associated microbes, and bruising of the tissues—should occur in combination. A splinter may give rise to tetanus without any contusion, the presence of a foreign body, carrying microbes, being sufficient. The conditions may, however, all be combined in the case of the more serious wounds received in war, in which shreds of clothing soiled with earth are embedded in the mutilated flesh.

Antisepsis and asepsis are therefore the chief prophylactics against tetanus ; since the time of Lister and Pasteur tetanus no longer occurs in surgical wards and lying-in hospitals. A wound should be carefully and gently washed with an antiseptic, which, if it does not destroy the tetanus spores, at least removes the foreign microbes. Cauterisation, which would aggravate the lesions in the cells, is not to be recommended, and nothing should be done which would in any way impair the vitality and natural means of defence of the tissues ; foreign bodies should be extracted, and lacerated wounds should be opened and freely cleansed. As the result of the progress in surgery, tetanus as a sequela of extensive wounds has practically disappeared ; it is more often seen to supervene upon small contused wounds, which have not aroused anxiety, or been thought to require attentive care.

The laws of phagocytosis explain, not only traumatic tetanus, but also a number of cases of the so-called medical or spontaneous variety, which most usually break out after a heat-stroke or

a chill, and where there is no wound or other channel of entry for the bacillus.

Excessive heat or cold debilitates the phagocytes, and weakens the organism's means of defence. In the case of a guinea-pig placed in a stove at a temperature of 42° C. (107·6° F.), the number of phagocytes in the blood diminishes, and those that continue to exist exhibit decreased vitality ; thus debilitated, the animal will not free itself from inoculated spores like a normal subject.

Two similar guinea-pigs are inoculated with equal doses of pure spores ; one is placed in a stove until the temperature reaches 42·8° C. (109·04° F.), the other is allowed to remain under normal conditions. The latter does not develop tetanus, but the other has an attack of an extraordinarily severe type ; the organism has been so profoundly modified by exposure to heat, that the tetanus bacillus has multiplied in its tissues and produced an infection, which never happens in natural tetanus. If, after keeping it for three months, we place the guinea-pig that proved resistant in the stove in its turn, it likewise develops tetanus. Where did the spores come from ? They are of the same kind as those to which our attention was drawn by Vaillard's experiments ; they remained over from the previous experiments, and the residue of latent spores was made to germinate by the application of heat (Vincent's experiments).

Insolation may have the same effect upon the soldier on the march as that produced on the guinea-pig by the stove. It is true that the soldier who develops "spontaneous" tetanus in this way never received an injection of tetanus spores, as the guinea-pig did in the laboratory. Yet, as the result of a wound or an excoriation of more or less old standing, there may have remained in his body a few spores, which did not germinate until the enfeebled system no longer defended itself against them. They were preserved in some inefficient phagocyte, which, instead of being a destroyer, was a guardian of virus ; and the heat-stroke played the part of an internal injury.

Cases of tetanus supervening upon injections of quinine are to be explained in the same way. In Madagascar it was found by naval surgeons that tetanus made its appearance after injections of this drug, and Émery-Desbrousses reports that, during the Madagascar expedition, eleven cases of tetanus occurred at

Majunga in less than a month, following upon injections of quinine. Dr. A. Laveran and Sir Patrick Manson, two of the foremost authorities on the pathology of malaria, have drawn attention to the cases of tetanus that may originate in this way; these cases, like those supervening upon heat-strokes, are of a very acute and sometimes foudroyant type.[1]

The spores are not introduced by the needle of the hypodermic syringe, for cases have been observed after strictly aseptic injections. Neither do the spores occur by accident in the bottles of solution used for injections; tetanus has resulted after the injection of products which were beyond all suspicion, and in fact the neutral chlorhydrate of quinine, the salt generally employed, has an antiseptic effect on the spores capable of preventing their germination. While numerous cases of "post-quinic" tetanus could be mentioned, it would scarcely be possible to refer to even one or two cases resulting from innumerable injections of cocaine, morphia, strychnine, or ether. The harmful result is due to the physiological action of the quinine, which, like lactic acid, weakens the defensive activities of the phagocytes.

If two guinea-pigs be inoculated, one with pure spores, the other with similar spores with the addition of quinine, the second animal alone develops tetanus. Supposing the quinine to have been inoculated four days before the spores, the guinea-pig's system has already eliminated it by the time that the latter are introduced, but tetanus still supervenes; the quinine has produced at the point of inoculation a kind of subcutaneous ulcer, a sore, or spot of less resistance, where the spores have germinated unmolested by the phagocytes, as in a contused wound. If the spores and the quinine be inoculated *at two opposite points* in the body, it is found that the spores disappear, as is always the case, from the spot at which they were inserted, but are met with again, and in numbers, at that at which the quinine was injected, the latter drug having induced at the seat of the injury the multiplication of the pathogenic bacillus (Vincent's experiments).

The conclusion arrived at by Vincent as the result of his researches is that, in the case of malaria patients who previously

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[1] H. Vincent, *Annales de l'Institut Pasteur*, December, 1904.

had neglected sores or excoriations, which might have permitted the entrance of the tetanus bacillus, it is advantageous to give a preventive injection of antitetanic serum conjointly with quinine.

We see, therefore, that "spontaneous" tetanus is due to the germination of spores which, after making their way into the system through some unknown channel, have remained there until a heat-stroke or chill has enabled them to elude the phagocytes.

There is as yet no reason to believe that tetanus spores are able to enter the system by way of the alimentary canal. Vincent did not succeed in producing tetanus in guinea-pigs, even very young and highly sensible ones, by causing them to swallow sharp fragments, such as nails and pieces of glass, copiously sprinkled with cultures of tetanus bacilli; and on the other hand we know that the tetanic toxin does not pass through the mucous lining of the digestive tract, and that tetanus does not result from swallowing the toxin. It would, however, be worth while to repeat these experiments, since within the last year or so attention has again been directed to the intestinal origin of infections.

It is common knowledge that diphtheria is cured by antidiphtheritic serum, and that tetanus is prevented by antitetanic serum, both of which are extracted from the blood of horses, which have been rendered immune to the respective diseases.

Antidiphtheritic serum is curative, antitetanic serum merely preventive; the terms "cure" and "prevention," however, have no meaning except in relation to the clinical signs of the disease. Physiologically both serums have a preventive action. The premonitory symptoms of diphtheria are of sufficiently early occurrence and definite enough for the doctor to intervene before the disease becomes too far advanced; the sore throat, false membrane, fever, and bacteriological analysis, give warning of the commencing intoxication, but the serum merely prevents fresh complications, and is of no avail against diphtheritic paralysis after it has set in. In tetanus there are no premonitory symptoms; when stiffness of the jaws sets in, the poison has already completed its passage from the peripheral nerve-endings to the centres, and has become firmly united with the nerve-cells. In order to cure tetanus, we should need

an agent capable of undoing this fixation or combination, and up to the present time there is no reason to believe that this is possible.

Serum-therapy originated in 1890, from von Behring's experiments. Its discovery would not have been possible unless Roux had previously found out the secret of toxic diseases. Von Behring's first guide was the classical memoir by Roux and Yersin on diphtheria, and, by repeating their experiments, Knud Faber had discovered the tetanic toxin. The proof that tetanus is a purely toxic disease had been furnished by the experiments of Kitasato and Vaillard.

Von Behring was guided by his personal belief, which is, however, a highly debatable one, that phenomena of immunity were to be met with, a view that was suggested to him by the action of the serum of the white rat on the bacillus of anthrax. The rat is very resistant to the latter disease; and since, outside the organism, in a test-tube, the anthrax bacillus is destroyed by rat serum, von Behring attributed the immunity of the rat to a bactericidal property of the serum, without the intervention of the white corpuscles: that is, *without phagocytic action.* He therefore believed in a "humoral" immunity, distinct from the phagocytic or "cellular" immunity already proved to exist by Metchnikoff, and he was disposed to seek in the humours, and especially in the serums of animals naturally or artificially immune to diphtheria, for example, a protective principle analogous to that observed by him in the serum of the white rat. The premiss, however, was false; if it be true that in a glass tube rat serum prevents the anthrax bacillus from developing, it does not prevent it from doing so in the organism of the living animal; the rat is not refractory to anthrax. Metchnikoff has proved beyond dispute that the relative immunity of the rat is due, not to bactericidal power in the serum, but to the activity of the phagocytes; and it had already been shown by Pasteur that the anthrax bacillus is killed by the humours of the rabbit, which is sensible to the disease, and develops on the other hand in those of the fowl, which is refractory. We know, however, that the reasoning that leads to great discoveries is not always flawless.

In order then to arrive at a system of serum-therapy, it was necessary to possess animals rendered artificially immune

to the toxins of diphtheria and tetanus. Pasteur had introduced vaccination against microbes by means of attenuated virus, so that, as soon as toxins were discovered, it was natural to attempt to vaccinate against these also. "Mithridatization" against certain poisons, by means of rendering the organism accustomed to minimal doses, had been known for centuries, and Mithridates himself is even said to have employed the blood of Pontine ducks, to which he had administered poisons. Mountaineers and horses in Styria are known to become accustomed to arsenic, just as morphiomaniacs do to morphia, and snake-charmers render themselves immune to venom by graduated inoculations.[1] When, however, animals are subjected to graduated inoculations with the toxins of diphtheria or tetanus, they are observed to waste away and die after receiving increasing doses. It was necessary to have recourse to attenuated toxins, just as Pasteur had made use of attenuated microbes. In order to attenuate the toxins, Fränkel heated them at 60° C. (140° F.), von Behring and Kitasato added trichloride of iodine, and Roux employed mixtures of toxin and iodo-ioduret solution; subsequently Calmette attenuated snake-venoms with hypochlorite of lime. Animals which are being rendered immune are not inoculated with pure toxins until able to tolerate the attenuated toxins.

Von Behring, then, found himself in possession of animals rendered refractory to tetanic toxin, with the idea that their immunity might be due to the properties of their humours, and when, after mixing together in a tube some toxin and a few drops of serum from an immunized animal, he observed that the toxin lost its power, he made the great discovery of antitoxic serums and serum-therapy. By his method serum-therapy consists in transfusing into a subject, suffering from

[1] "Even in France we are acquainted with professional viper-catchers, who employ the method of graduated inoculations in order to render themselves immune to the bites of indigenous reptiles. One of these men, who lives near Arbois (Jura), takes good care to get himself bitten, at least once a year, by a young viper; when he forgets this precaution and happens to be bitten, he always feels the effects much more severely." A. Calmette, "Venoms, Venomous Animals, and Antivenomous Serum-Therapeutics" (p. 234). English edition, translated by Ernest E. Austen. London: John Bale, Sons and Danielsson, Ltd., 1908.

or threatened with a disease, serum from an immunized animal. It should in justice be remembered that this transfusion had already been tried by Richet and Héricourt, who had pointed out the preventive power of the blood of animals rendered refractory to a microbic disease studied by them. Here, however, there was no question of antitoxic serum ; the discovery of antitoxic serums belongs to von Behring.

It was announced in December, 1890, in a short note signed by von Behring and Kitasato, and consisting of but a few lines, as follows :—

"The serum of a rabbit immunized against tetanus possesses the property of destroying the tetanic poison.

"This property exists both in the blood drawn from the vessels, and in the serum after being separated therefrom. It is lasting, and the serum produces its effect even in the organism of other animals ; it is therefore possible to exert a therapeutic action by the transfusion of the blood or serum.

"The antitoxic property does not exist in the blood of animals which have not been rendered immune to tetanus."

Prolonged work, tests and technical improvements were still necessary, and some years elapsed before the laboratory experiments resulted in the therapeutic method commonly applied to man at the present day. Antidiphtheritic serum-therapy only achieved success in the hands of Roux in 1894.

In their earliest papers, it was stated by von Behring and Kitasato that antitetanic serum appears to be incapable of curing acute tetanus in mice, but that in less severe though fatal cases, when the symptoms are already well marked, as in the case of a mouse which is bound to die in some hours time, the serum effects a *cure.* When, however, serum-therapy was applied to tetanus in human beings, the "cures" were of the most questionable character. The matter was settled by Roux and Vaillard, who showed that antitetanic serum does not cure tetanus after it has set in, but that it infallibly prevents it. Since then, preventive injection of serum is the rule whenever a man or horse receives an injury from which tetanus may result.

The preparation of antitoxins is a difficult undertaking, which can only be accomplished successfully by practised hands, under the control of specialists. Tetanus is the toxic

disease *par excellence*, and there is no antitoxin more active than antitetanic serum. The activity of the antitoxin corresponds to that of the toxin : the antitoxic strength of the serum issued by the Pasteur Institute is 1 in 1 milliard, which means that it is sufficient to inject into a mouse a quantity of serum equal to one milliardth of its weight to protect it from the lethal dose of toxin ; a man receives an injection of 10 cc. The immunity conferred by the injection lasts from a fortnight to six weeks ; if the wound take longer than this to heal, and if the medical attendant be afraid that tetanus bacilli remain in the still contused and suppurating tissues, the injection of serum must be repeated.

Nothing has been said against antidiphtheritic serum, but tetanus antitoxin is sometimes tacitly discredited, because it does not effect a cure. All scepticism in this respect is unjust and criminal ; the preventive action of the serum being infallible, where is the doctor who would lightly incur the remorse of not having prevented a case of tetanus? The rapid cure of a deadly disease astonishes the senses, and produces the effect of a miracle ; this is the case with diphtheria antitoxin. Preventive efficacy makes less impression because direct proof is wanting. It is impossible to prepare a tabular statement with reference to human beings suffering from tetanigenic wounds, and to write "would have developed tetanus," or "would not have developed tetanus," opposite each name. In default of statistics relating to human beings, however, we have information as regards horses, eloquent figures having been compiled by Nocard.

Since 1897, Nocard has made a collection of 3,088 cases of animals, including 2,708 horses, inoculated preventively after a surgical operation or an accidental wound ; he divides them into two groups. *First group :* 2,500 animals inoculated immediately after the operations usually complicated by tetanus (castration, docking of the tail, umbilical hernia). *Second group :* 600 animals treated one, two, three, four days *and more* (that is to say, sometimes quite a long time) after a polluted wound, such as a gash from the tooth of a harrow, or an old nail, a quitter, &c. Out of this total there was a single case of tetanus, which occurred in a horse which it was impossible to inoculate until five days after the wound was inflicted (by

a farrier's nail) ; the disease was of a mild type and the animal recovered.

During the same period of time the veterinary surgeons who noted the history of these animals observed, in animals that had not been treated, 314 cases of tetanus, 220 of which were in horses. "The results," adds Nocard, "are the more convincing, seeing that the treatment is applied in all cases in places or surroundings in which tetanus exists." Some statistics by Labat include 703 solipeds injured or operated upon under conditions in which tetanus is to be apprehended. None of the animals treated became infected, but among the *few animals* not inoculated three developed tetanus.

Tourists and motorists, who often spend whole days in countries where assistance cannot be obtained, would do well to include in their outfit a few bottles of tetanus antitoxin. No other remedy exists, but obviously it does not dispense with the necessity for antiseptic or aseptic precautions. Of the drugs in former use, the only ones that should be retained are the anodynes, such as chloral, which deaden the agonies of the patient by rendering him unconscious. It is no disrespect to medicine to forget all the rest.

Vaccination against small-pox was discovered by Jenner at a time when science was incapable of explaining the natural or acquired immunity of an organism to an infectious disease. After thirteen years of experimental research science has not yet furnished us with the complete explanation of the action of antitoxic serums ; the discovery of serum-therapy was therefore a case in which practice anticipated theory.

"Antitoxin" is the term employed to designate the substance that acts against toxin, and is contained in the serums that we inject. It is unknown in the pure state, we are ignorant of its chemical composition, we know not how to prepare it, and we cause it to be produced by living animals ; it is consequently not surprising that its action is still mysterious.

At first sight it appeared impossible to imagine resistance to toxins as being resistance to microbes. What could be the action of the phagocyte, that destroys formed elements, toward a soluble poison ? Is there any question of phagocytes in the case of habituation to a venom, or to a definite chemical compound, such as an arsenate ? Serum-therapy would seem to

introduce into medicine the notion of an antitoxic immunity entirely different from immunity to microbes.

The conception that first suggested itself was a chemical one. The antitoxin would neutralize the toxin by combining with it, as an acid combines with a base to produce a salt. In the humours of animals naturally refractory to tetanic intoxication, in those of animals artificially immunized, and in the case of a wounded man who receives a preventive injection, the antitoxin combines with the toxin to form an unknown and atoxic compound, and the organism is preserved. From this conception arose the "immuno-chemistry," or chemistry of immunity, of Arrhenius, which seeks to apply the laws governing chemical combinations to the reactions of substances, the chemical nature of which is so obscure. It treats the phenomena that take place in the organism as being of the same nature as those that occur in a flask or a test-tube ; it is, if we will, a mechanical theory of immunity.

From the very commencement of serum-therapy, however, it was impossible not to recognize that the organism intervenes actively in the reactions of immunity, and that it is not an inert vessel used in experiments. So long ago as 1894, it was thought by Roux that antitoxic serum must bring cells into play.[1] Little by little phagocytosis, the "vitalistic" conception of Metchnikoff, forced itself upon the minds of investigators as affording the explanation of antitoxic as well as of antimicrobic immunity. Without denying the action of the antitoxin on the toxin, it was recognized that it could not take place without the intervention of the phagocytes. The day may come, perhaps, when science will possess a purely chemical explanation of immunity ; in the present state of our knowledge, however, the vitalistic explanation is the truer one.

That antitoxin neutralizes toxin is true on the whole ; but this action is not sufficient to account for all cases of antitoxic immunity. There may be immunity without antitoxin, and antitoxin may exist in animals which are not immune.

The scorpions of Algeria and Tunis are capable of receiving, without exhibiting the slightest morbid symptom, 1,000 doses, lethal to the mouse, of tetanic toxin, but the blood of

[1] *Sur les Sérums antitoxiques:* a communication made to the Congress at Buda-Pesth, 1894.

scorpions endowed with this immunity has no antitoxic power. When the toxin is injected into a tortoise, it is retained for a long time without causing any ill-effects, and without conferring any antitoxic property on the creature's blood. Alligators, which are refractory to the toxin, produce antitoxin freely, though slowly, and young individuals, in particular, resist the toxin for a long time (for weeks) before antitoxin appears in their blood (experiments by Metchnikoff). The fowl is extraordinarily resistant to tetanus poison, and yet fowl serum never exercises a neutralizing effect on the toxin (Vaillard's experiments).

Immunity to tetanus can be produced in the rabbit without the antitoxic property appearing in its blood (Vaillard's experiments). It has been noticed by M. Prévôt, Director of the Serotherapeutic Station of the Pasteur Institute at Garches, that the yield of antitoxin is unequal in the case of horses, which have been treated in the same manner and have acquired the same immunity. In a large number of horses, it happens fairly often that certain individuals, without being particularly sensible to a given toxin, show themselves incapable of producing the corresponding antitoxin.

Animals in which the process of rendering them immune to toxin has been carried to great lengths may, in spite of the abundance of antitoxin in their blood, die of intoxication (numerous observations by Roux, Vaillard, von Behring, and Kitashima). Brieger has published the case of a goat strongly immunized to tetanic toxin, which yielded good antitetanic serum and even antitetanic milk, and yet, after receiving an injection of toxin slightly stronger than before, died of typical tetanus.

In short, "we see clearly that immunity to toxic substances is a highly complex phenomenon, which it is impossible to consider as simply an antitoxic function of the humours. It is for this reason that we cannot accept the theory according to which it is attempted to confine this category of immunity within the narrow limits of a mere reaction between two substances, entirely comparable to what is observed in a test-tube."[1]

So long ago as 1893, Buchner showed, by means of an

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[1] Metchnikoff, "L'Immunité dans les Maladies infectieuses," p. 395.

excellent experiment, what a mistake it is to speak of neutralization, in the chemical sense, of toxin by antitoxin. The guinea-pig is more sensible to tetanus poison than the mouse, that is to say that less toxin is required in order to produce tetanus in 500 grammes of guinea-pig than is requisite to produce it in the same weight of mouse. A mixture of toxin and antitoxin is prepared, which is innocuous, that is *neutral*, in the case of the mouse ; this mixture, when inoculated into the guinea-pig, gives it tetanus ! This experiment was repeated and varied by Roux and Vaillard : a given mixture of toxin and antitoxin, which is tolerated without ill-effects by normal guinea-pigs, gives tetanus to guinea-pigs of the same weight whose resistance has been lessened by previous experiments. If the antitoxin destroys the toxin, why these differences ?

"Is not the natural explanation of these facts," writes Roux, "to be found in the action of the serum on the cells rather than on the toxin ? The cells of the fresh guinea-pigs, being in full vigour, respond to the stimulation of the serum, and are, as it were, indifferent to the toxin, to which those of the guinea-pigs already affected by previous experiments succumb." What cells are here referred to ?

It was formerly thought by Ehrlich that the antitoxin is secreted by the cells that are sensible to the toxin. Since tetanus is a poisoning of the nerve-cells, it is therefore the nerve-cell that furnishes the counter-poison. The correctness of this view was apparently proved by an experiment which made a great sensation in laboratories ; we refer to the famous experiment of Wassermann and Takaki. If brain substance from the guinea-pig be pounded up with tetanic toxin, the mixture is no longer toxic ; the nerve-cells have therefore neutralized the antitoxin.

The fact is as stated, but the interpretation is false. Wassermann's experiment destroyed the theory that it was intended to prove, and the answer was not long in coming. If the brain be the source of antitoxin, toxin introduced directly into the brain of the living animal ought to be immediately neutralized ; but it is the contrary that happens. The guinea-pig is extremely sensible to the smallest doses of toxin inoculated in the brain ; and not only do *fresh* rabbits develop tetanus when thus treated, but even rabbits *immunized* against tetanus ! The brain of an immunized animal is not immune (experiments by Roux and

Borrel on cerebral tetanus, 1898). The neutralization obtained *in vitro* with the cerebral substance of the guinea-pig is produced by fatty matters, such as cholesterin, which form an integral part of it ; an analogous result is produced by means of carmine, which is derived from the fat-body of the cochineal insect.

Why is it that the rabbit tolerates without ill-effects fairly strong doses of toxins inoculated subcutaneously, while extremely sensible to a minimal dose inoculated into the brain ? The reason is that poison inoculated under the skin is destroyed *en route*, and does not reach the brain-cells. Before coming in contact with the sensible cells it must be arrested by cells which are less sensible and capable of neutralizing it. "What are these cells ? Perhaps the phagocytes that, under many circumstances, are seen to be able to destroy the poisons contained in the bodies of microbes. We cannot vouch for it, but it seems to us that the problem of immunity to microbes and that of immunity to toxins will receive similar solutions."[1]

Since the foregoing extract was written, arguments in support of the theory therein contained have multiplied. It is the phagocytes that arrest the toxins before they reach the sensible cells ; phagocytes, according to Metchnikoff, must not be considered as cells capable only of seizing the bodies of microbes and animal cells, and as elements that always give way before poisons. It is precisely these cells that are most resistant to toxic substances, and that protect the higher cells against poisoning. Metchnikoff has, moreover, advanced the hypothesis that certain phagocytes, by transforming the toxin that they have absorbed, produce the antitoxin.

When a patient receives antitetanic serum, his phagocytes are rendered better qualified to attract the toxin originating from the wound, to destroy it, and perhaps to transform it into antitoxin. The resistance of the patient is due to the impulse or stimulus thus imparted to the leucocytes. The activity of the white blood corpuscles, expressing itself in different ways, ensures immunity, natural or artificial, to infectious and toxic diseases.

[1] Roux and Borrel. "Tétanos cérébral et Immunité contre le Tétanos," *Annales de l'Institut Pasteur*, 1898. The same authors, in making generalizations from their experiments showed that identical facts are observed in connection with poisons such as atropine and morphia.

SLEEPING SICKNESS.

On October 25, 1906, a French expedition started from Bordeaux for Brazzaville, in French Congo, for the purpose of studying sleeping sickness.[1] Organized by the French Geographical Society, and under the scientific direction of the Pasteur Institute, its special instructions were drawn up by scientists such as MM. Laveran, Bouvier and Giard. It received a grant of 200,000 francs (£8,000), of which half was provided by subventions from the French Colonial Office and the Commissary-General of the Congo, and the remainder by the Geographical Society, the French Anti-slavery Society, various maritime and mercantile societies, and a few private donors. The moment was propitious. Six years ago next to nothing was known as to the cause and mode of transmission of this mysterious disease. To-day we know that it is epidemic and of parasitic origin ; the pathogenic organism and the mode of propagation are known, and something has been done towards discovering a cure for a malady which at the present time constitutes the most urgent problem in tropical medicine and hygiene. There is reason to hope that Equatorial Africa will be delivered from the scourge that is threatening the progress of colonization ; and, since white men living in Africa are liable to contract the disease, it is confidently to be expected that European nations will lend their active support to the work in hand.

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[1] The expedition consisted of Dr. Gustave Martin, surgeon-major of colonial troops, who distinguished himself by his recent expedition in French Guinea ; Dr. Le Boeuf, surgeon-major of colonial troops, and MM. Roubaud and Weiss, as naturalist and assistant naturalist. For some years past England has provided funds for the work of its Sleeping Sickness Commission. The King of the Belgians has established a research fund of 300,000 francs, and an international prize of 200,000 francs for the discoverer of the cure. In 1907 a German expedition, under the distinguished leadership of Professor Koch, was at work on the shores of Lake Victoria.

A negro attacked by sleeping sickness exhibits symptoms so singular as to have attracted the attention of early observers, and in 1803 an Englishman, named Winterbottom, gave an account of them as seen by him in Sierra Leone. The spectacle of abandonment, solitude, and misery makes a deep impression upon the traveller; left to himself, in the open or thrust into a hut,[1] as though suffering from a contagious disease, the victim lies, with his body half covered with ashes, stupefied and drowsy. It is a case of somnolence rather than sleep: he hears, and makes an effort to open his eyes, but the heavy lids refuse to rise; all the muscles are weak and flaccid, and will-power is at an end. The appearance of sleep is mainly due to the closing of the eyelids and the muscular weakness. Though stupefied by day, patients often become restless at night, and a prey to excitement and delirium. "In certain cases," writes Dr. Brumpt, who crossed Africa in 1903, with the Bourg de Bozas Expedition, "in apparently healthy individuals, hypnosis sets in with an attack of acute mania, with homicidal impulses; on being taken to prison and fettered, the individual falls into a comatose condition, which necessitates his transference to hospital, after which all the symptoms characteristic of sleeping sickness gradually become established."[2]

The symptoms are well known to medical men in Tropical Africa: violent pains in the head and down the spine,[3] a dragging gait, which precedes the period of paralysis, unprovoked fits of weeping, and apparently causeless changes in the character. Yet other symptoms, which do not appear to be the most serious, are perhaps the surest: trembling of

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[1] "Many patients, relegated to the obscurity of huts, escape the vigilance of the doctor. . . . When a person is attacked, people avoid him through fear of contagion and the relatives alone attend to the poor wretch, for whom a special calabash is reserved" (Dr. Gustave Martin, "Les Trypanosomiases de la Guinée française," Paris, Maloine, 1906). "The patient is now (final period) carried to a distance from the village, into the bush, where he is left to die of starvation through fear of contagion" (letter from Captain Foureau quoted by A. Laveran, *Comptes rendus de la Société de Biologie*, October 28, 1905).

[2] *La Nature*, April 28, 1906.

[3] "By an expressive piece of dumb show, the natives indicate that patients suffer as though they received blows on the head from a hammer" (letter from Captain Foureau, quoted by Laveran).

the tongue, hands and arms; coldness of the skin; swelling —without suppuration—of the lymphatic glands of the neck, axilla and groin; accelerated pulse and respiration, and fever with great fluctuations in temperature. On the approach of death, the attacks of somnolence become more frequent and more profound; the temperature falls below the normal, and the patient passes away in a comatose condition.

"At Kouriah, in Filacounji, there is a man who has been suffering from sleeping sickness for the last three years. He is very weak, staggers as he walks, and trembles all over; he can stand upright with his eyes closed, but cannot walk straight; he replies to questions put to him by our interpreter. For the past two months he would seem to have been better, since formerly he fell asleep while eating and even while walking.

"At Telimele, they brought me a patient with a dull expression and a difficulty in walking, who for the last two years is said to have had an invincible tendency to sleep. He is very soon fatigued, and speaks in low tones, and as seldom as possible: he formerly read the Koran, but his sight has steadily deteriorated, and he has done no work since the commencement of the disease. He complains of violent headaches; the glands in the neck are inflamed, and those in the groin as well.

"At Toubah, I was taken to see one of the villagers, a youth who passes day and night in profound sleep, and only shakes off his somnolence at mealtimes. When we made him talk, he replied with difficulty; he has a fixed look, devoid of expression; he is incapable of walking for even a short distance, and totters on his feet. The temperature is normal, but the pulse is small and rapid; there is some incontinence of urine and fæcal matter; the glands are enlarged."[1]

Symptoms such as these indicate that the central nervous system is affected. In infants the disease often resembles acute meningitis; the child has cervical opisthotonos, that is, it lies with the head thrown back on the nape; in the case of adults as in that of children, an autopsy shows that the meninges are inflamed.

[1] Dr. Gustave Martin, *op. cit.*

As the result of prolonged and close observation, doctors have discovered that sleeping sickness is but the last stage of a much more chronic disease, which for a very long time only shows itself in attacks of fever and the enlargement of the glands of the neck. The commencement of the nervous symptoms and slight attacks of somnolence are separated from the comatose condition and death of the patient by an interval of four, six, or eight months, or, in exceptional cases, more than a year. It is now known that the first nervous and cerebral symptoms appear in subjects who, for months and even years, have suffered from an intermittent fever, the attacks of which are very different from those of malaria. Before the attack there is no shivering fit, and after it is over little or no sweating; *quinine is of no avail;* the lymphatic glands are enlarged (adenitis); the action of the heart is accelerated (tachycardia); the face is somewhat puffy, and, like the body, is sometimes covered with red patches. Nothing more is to be noted, and even these symptoms are well marked only in white people and mulattoes; in negroes they are frequently absent.

This febrile condition, which precedes the disease, may continue for years. A French medical man named Guérin, who made observations in the Antilles about 1865, reported cases of sleeping sickness in negroes who had left Africa five or six years previously, and could only have contracted the malady in their native land, for it does not occur in the West Indies. Blacks from the Island of Goree, who had spent some time at Casamance, in Senegal, where the disease is rife, did not consider themselves safe until at least seven years had elapsed since their departure from Casamance. African natives have all along been aware that the disease is the final stage of an illness which lasts for years; the discovery of the parasite has confirmed the correctness of their observations. Death may supervene after a variable period of somnolence; if a patient receives no treatment the disease is always fatal.

It is natural to enquire for how many years or centuries sleeping sickness has prevailed in the parts of Equatorial Africa in which it is endemic. White people have come, have stirred up the different races, opened up the country, disseminated the sickness, and are now dismayed at its progress. The sleeping sickness zone may be indicated by taking a map of Africa and

tracing on it two sinuous lines, one on either side of the Equator ; that on the north would run approximately from Dakar, in Senegambia, to Mombasa, passing through Kayes, Lake Chad, Lake Albert, and Uganda ; that on the south would extend from Benguella to the mouth of the Zambesi. The disease is spreading from three great endemic foci ; the first, and least important, lies to the north of the Gulf of Guinea. and includes Casamance, the hinterlands of French Guinea, Sierra Leone, the Ivory and Gold Coasts, and Togo, as well as Yatenga, Benin, and several localities in Cameroon ; the second includes, in French Congo[1] and the Congo Free State, the banks of the River Congo, from Stanley Pool to Nouvelle Anvers, the region of the Cataracts, and the banks of the Kasai, and also, further to the south, Angola ; the third focus is Uganda.

The invading march of the malady is following a general west-to-east direction, from the Atlantic to the Indian Ocean ; the regions menaced at the present time are Darfour and the Anglo-Egyptian Sudan, and the entire East Coast of Africa, from Somaliland to Zululand. The extension of the disease has been assisted by the following factors : movements of populations ; wars ; the activities of Samory's raiders ; the disbanding by Stanley, in 1888, of the Sudanese soldiers after the rescue of Emin Pasha (resulting in Uganda becoming infected) ; famines (islands in Lake Victoria, in 1901-1902—increased mortality) ; exploring expeditions and caravan routes ; the section of the Uganda Railway near Lake Victoria is already infected. In the Congo Free State the influence of the transport routes has been well traced by Dr. J. L. Todd. Before Europeans came into the country, about the year 1884, the disease was confined to the region of Lower Congo and did not extend above Bumba, which may be taken as marking the most northerly point of the great bend made by the river. The white men introduced steamers on the Congo, assumed control of the caravans and portage, and shortened distances ;

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[1] In French Congo, the disease is common on the French bank of the Congo and the Ubangi, and in Loango : it is still rare at Libreville, and in the valleys of the Ogowe, and Upper Sangha (Kermorgant, *Annales d'hygiène et de médecine coloniales*, 1906, pp. 126-141, and map).

the natives, of both sexes, passed from the infected to the non-infected regions, and the disease went with them. In 1897, twelve years after the foundation of the Free State, cases of sleeping sickness were noted in the districts round Luluabourg and Lusambo, which were not infected in 1884.

"The caravan routes between Lusambo and Kasongo were formerly much used. It was along these routes that the troops directed against the Arabs advanced. Caravans carrying supplies to the posts in the eastern part of the Free State passed over the same roads, which were also used by native Arab traders. From Kasongo to Baraka and Albertville on Lake Tanganyika go very important caravan routes, over which pass the whole of the supplies to the region about Lake Kivu, and Lake Tanganyika. In 1896 the caravan route between Lusambo and Kasongo was closed, and the transport between the east and west of the Free State went instead up the Congo in steamers to Stanleyville, and thence by canoes to Kasongo. . . . Sleeping sickness has spread along the most important overland routes, and up and down the Congo from Kasongo, until there are only comparatively small stretches of river between Stanleyville and Kasongo still uninfected. . . . All these imported cases are soldiers, labourers, or their wives, brought long distances from their homes, as a direct result of the opening up of the country by Arabs and Europeans."[1]

The ratio of cases of the disease to population is extremely difficult to determine, but the following figures are instructive. In Togo, according to Hintze, 48 deaths took place at Worawora, from 1896 to 1903, while in seven infected localities there were 35 deaths in 1903 alone. Two Belgian doctors, named van Campenhout and Dryepondt, have kept a record of the cases of sleeping sickness that have occurred in the mission school at Berghe-Sainte-Marie, at the confluence of the Kasai with the Congo: the death-rate was 13 per cent in 1896, 19 per cent. in 1897 ; from 22 per cent. to 39 per cent. in the following years, and 73 per cent. in the first quarter of 1900. Writing on October 15, 1906, Koch stated that the population of the Sese Islands, in Lake Victoria, which was estimated at 30,000 at the time of the arrival of the missionaries, had fallen

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[1] John L. Todd, *Lancet*, July 7, 1906.

to 12,000 owing to sleeping sickness. He visited a village which formerly had 200 inhabitants, and found only 55 ; on making a careful examination of 22 of these, it was discovered that 17 were infected. In a family of five, consisting of father, mother, and three sons, all but the mother were already doomed. Koch estimates that 70 per cent. of the present population of the Sese Islands are infected ; and since some of those infected do not yet exhibit even the earliest symptoms, the proportion of those suffering from the disease may be fixed at 80 per cent. At the date of Koch's communication, the disease was especially prevalent in the islands in the northern part of the Lake, while the southern shores were still free from it. At Muansa, on the German shore of the Lake, in a population of 8,000, Koch had not met with a single certain case of the disease. It was, however, only a question of months ; on April 25, 1907, Koch wrote that he had found cases in German territory at the two extremities of the equatorial diameter of the Lake, in Shirati and Bukoba. On September 5, 1907, Koch reported that Drs. Feldmann and Breuer were already treating 200 cases at Shirati, and he feared that the disease would shortly invade the large island of Ukerewe, which lies in the southern part of the Lake, and contains 30,000 inhabitants.

The colonization of Africa will be impossible unless sleeping sickness be stamped out.

Not many years ago, it was stated in the newspapers that the germ of the disease is given off by the foliage of certain tropical trees, but nothing more has been heard of this hypothetical manchineel. Food also was incriminated ; the negroes were said to be intoxicated by the manioc root, which they often eat raw or scarcely cooked. Yet little or no manioc is eaten in Casamance, where the disease is common, while it is eaten freely in Dahomey, where sleeping sickness is extremely rare. Since the malady is especially prevalent on the banks of rivers and lakes, suspicion fell upon certain fishes which are caught in the mud ; but the disease is not endemic in many countries in which fish, and that of the same kinds, is eaten to an equal extent.

On the commencement of the epoch of micro-organisms in medicine, search was made for the microbe of sleeping sickness,

and, as has frequently happened in the case of other infectious diseases, investigators found, not one but several microbes: bacilli, diplococci, and streptococci. One of these even received the name of hypnococcus; since it had been found in the cerebro-spinal fluid, a thin sheet of which, enclosed between meninges, covers the nervous centres, it seemed likely that it was the cause of the symptoms of a nervous and cerebral disease. The experiments made in order to confirm the discovery were unconvincing, and, indeed, all these various microbes were merely the results of "secondary invasions."

It was suggested by Sir Patrick Manson, one of the most distinguished authorities on tropical diseases, that sleeping sickness was caused by minute worms, known as *filariæ*, which live in the blood; but though it is true that filariæ are found in many patients, they are by no means invariably present, and Manson's hypothesis was accordingly abandoned. The suggestion was an original one, in that its author pushed his investigations beyond the realm of bacteria into that of animal parasites. Bacteria are unicellular organisms which belong to the vegetable kingdom, while the protozoa are unicellular organisms belonging to the animal kingdom, some of which also give rise to diseases. For a very long time, indeed, the causative agent of malaria was sought for among the bacteria, until the day when Laveran discovered the protozoon, that lives as a parasite in the red blood corpuscles of those suffering from the disease—a grand discovery, which was opposed to the ideas then current, and revealed to science a new world. To this world belong micro-organisms causing terrible diseases among animals, which are the despair of stock-breeders in Asia, Africa, and elsewhere, such as *surra* in horses and camels, *nagana* in horses and cattle, *dourine* in horses in Algeria, and *mal de caderas* in horses in Argentina. These micro-organisms are known as *trypanosomes*.

On May 10, 1901, Dr. R. M. Forde, medical officer of the hospital at Bathurst, in the Gambia Colony, was called upon to treat a European, aged 42, who was suffering from a fever with peculiar symptoms—in reality the first stage of sleeping sickness. Forde examined the blood for the malarial parasite—Laveran's hæmatozoon—and found instead a kind of microscopic and extremely active vermicule, which he did not know and could

not identify. A few months later he again saw both patient and parasite, and showed the latter to the late Dr. J. E. Dutton, who had a more extensive knowledge of diseases caused by trypanosomes. Dutton at once recognized that the active vermicule was a trypanosome, named it *Trypanosoma gambiense*, and thought that it was the cause of this febrile disease, that did not resemble malaria.

In 1903, Dr. A. Castellani, an Italian medical man in the service of the British Government, found trypanosomes while making a microscopical examination of the cerebro-spinal fluid of natives in Uganda suffering from sleeping sickness.[1] Castellani's discovery was verified by Colonel (now Sir) David Bruce, who has become celebrated owing to his work on diseases due to trypanosomes, and especially on *nagana*. The new trypanosome, which appeared to be, indeed, the cause of sleeping sickness, received the name of *Trypanosoma ugandense*.

There seemed reason to believe that there were in Africa two diseases due to trypanosomes : Firstly, a febrile malady of an intermittent type, distinct from malarial fever, and caused by the Gambia trypanosome ; secondly, sleeping sickness, caused by the trypanosome of Uganda. Further observations were made on both diseases ; the initial discoveries were confirmed, and a trypanosome was found in numerous cases of continuous fever and sleeping sickness. Bruce, among others, observed it in the cerebro-spinal fluid of sleeping sickness patients thirty-eight times in thirty-eight cases, and twelve times out of thirteen in the blood.

The idea now suggested itself that the two diseases were related, and that the fever precedes the somnolent period. There also naturally arose the question whether the two phases of one and the same morbid manifestation were due to two distinct parasites, or whether the two parasites—that of the Gambia and that of Uganda—were not rather one and the same trypanosome, the pathogenic agent in a long infection of which sleeping sickness is but the final stage. The two parasites were studied in the Congo Free State and in Uganda, and found to be identical in form. By good fortune they were

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[1] *British Medical Journal*, May 23, 1903 : Castellani announced his discovery to the Royal Society of London in a letter dated April 5, 1903.

inoculable into various species of animals, and it was thus possible to bring them to Europe, study them at leisure in laboratories, and cause them to multiply by means of serial inoculations. The trypanosome from Uganda and that from the Gambia were found to be inoculable into the same species of animals, and to have the same pathogenic action; everything pointed to their specific identity.

The decisive observation—the "crucial fact"—was, however, still lacking. A patient had to be kept under observation for months, or if need be for years, in order to see the febrile stage develop into the lethargic one, to make a periodical examination of his blood and cerebro-spinal fluid, and to discover whether the same trypanosome was constantly present. The requisite case, celebrated in scientific literature under the name of Manson's case, was provided by chance; the unfortunate victim was a white woman, who, in August, 1901, was attacked at Monsembe, on the Upper Congo, by "trypanosome fever." This lady returned to England in November, 1902, was on several occasions admitted to the branch of the Seamen's Hospital in connection with the London School of Tropical Medicine, and finally died on November 26, 1903, in a state of lethargy and coma; she had been kept continuously under observation, in Africa as well as in London, by specialists of repute, such as Daniels, Low, and Manson.

Trypanosomes were seen in the blood for the first time on October 27, 1902; since that date they were *almost always found* by Daniels and Manson, provided that the examination was continued for a sufficient length of time. There was a striking similarity between the symptoms exhibited by this lady and those noted by Forde and Dutton in the case referred to above. Towards the middle of October, 1903 (after several periods of temporary improvement, followed by relapses), there was noticed for the first time a "tendency to drowsiness." The patient "was in bed, extremely weak, very much wasted, with a rapid pulse, which she had had all along, and some fever. . . . The trypanosomes were somewhat more numerous in the blood. She was emotional, but could converse for a short time intelligently, only, when conversation stopped, she would close her eyes and appear to sleep. . . . From that time the patient's condition gradually got worse;

drowsiness increased, conversation became confined to monosyllables, occasionally food was retained in the mouth for a considerable time before it was swallowed, the sphincters were no longer under control, spasm of one arm occurred, bedsores formed, and she died comatose on November 26."

A necropsy made the same day showed "macroscopic signs of chronic meningo-encephalitis, injection of vessels, and milkiness of the pia arachnoid. . . . Subsequently microscopical examination of brain sections by Drs. Mott and Low revealed the extensive perivascular small mononuclear infiltration so characteristic of sleeping sickness."[1]

This case, corroborated as it has been by more recent experiments, especially those of Laveran, demonstrates the unity of trypanosome disease throughout its course, and finally proves the identity of the two trypanosomes, found respectively in the Gambia by Forde and Dutton, and in Uganda by Castellani and Bruce. Sleeping sickness is the final stage of an infection, which should be termed human trypanosomiasis ; the pathogenic organism must retain its earlier designation, *Trypanosoma gambiense*.[2] Europeans are attacked by the disease, but only in Africa ; why this is so we shall shortly see.

The trypanosome of sleeping sickness is a *microbe*, in so far as the term is used to designate any living organism which can only be seen by aid of the microscope. It is not, however, a bacterium, that is to say an organism consisting of a single vegetable cell, like the bacilli of anthrax, typhoid fever, and tuberculosis. A trypanosome is an animal cell, a protozoon, like the microbe of malaria, from which nevertheless it differs greatly ; the sub-class *Flagellata*, to which it belongs, is related to the *Infusoria*, which are found in water, and can be cultivated in infusions of hay and other vegetable matter ; the first known trypanosome was discovered in 1841. Even before they were found to be responsible for sleeping sickness, these parasites earned an unenviable reputation, and provided one of the most important sections of tropical pathology by being

[1] *British Medical Journal*, May 30 and December 5, 1903.

[2] Since "Manson's case" a number of other cases in white people have been reported, and the Pasteur Hospital in Paris has had an almost constant succession of them. The records of fifty years ago make mention of cases in mulattoes and mestizoes.

the cause of *nagana* and *surra*, the great epizootics of hot countries.[1]

If a drop of infected blood be examined under the microscope, the trypanosomes will be seen making their way among the red corpuscles, and looking like small elongate vermicules. They are extremely active, double over, curl round, or swim about, turning upon their axis like a gimlet or an auger. They might be thought to be playing at bowls with the blood-corpuscles, to such an extent do they buffet them and make them turn and jump. When they are fixed upon a microscope slide and stained, their structure can be seen ; under high magnification there may then be observed a minute fusiform body, along the whole length of which runs a membrane, which is attached by one of its edges, while the free margin is bordered by a filament or flagellum ; membrane and flagellum together represent the organ of locomotion, the oar, rudder, or whip which, in the living animalcule, produces such extraordinary activity. This flagellum, which runs along the free edge of the undulating membrane, starts from a small nucleus contained in the spindle-shaped body, and situated near its posterior extremity. At the other or anterior extremity, it detaches itself from the membrane and floats free. A second and much larger nucleus is to be seen near the middle of the body. The average length of the microbe is from twenty-five to thirty thousandths of a millimetre—about four times the diameter of a red blood corpuscle, while its breadth is one-third of that of a corpuscle. The trypanosome multiplies by dividing longitudinally into two, and the new individuals divide again in their turn, and so on ; this process may often be seen in operation under the microscope, in a drop of blood.

A patient's illness dates from the day on which the trypanosome enters his blood ; after a period of incubation lasting for three months, intermittent and irregular attacks of fever set in, which are refractory to quinine, and may continue to recur for years ; blood taken from a superficial puncture during an attack contains trypanosomes; but, as a general rule, there are none

[1] The only general work on trypanosomes is "Trypanosomes et Trypanosomiases," by Laveran and Mesnil (Paris, 1904), an excellent volume, of which an English translation, with additions, was published by Nabarro in 1907.

during the intervals. The second stage of the disease, in which the nervous phenomena and lethargy are superadded to the fever, commences when the parasites penetrate into the lymphatics and blood-vessels that permeate the meninges, and envelop the brain and spinal cord, so that the central nervous system is bathed with blood and lymph containing trypanosomes. Owing to their presence, and doubtless also to the toxins secreted by them, they produce inflammation of the meninges and degeneration of the nerve-cells; death may supervene before the period of lethargy.[1]

In the second stage of the disease, spontaneous recovery is unknown, and the majority of observers doubt whether it ever occurs in the stage of fever. The differences between the two stages are not always sharply defined; towards the end there may be fever, lassitude, and exhaustion, without lethargy. The deep and continuous sleep is scarcely met with in the Congo region, where the disease is not marked by the epidemic and invading characteristics seen in Uganda. In the same patient, the malady and the number of parasites, both in the blood and in the cerebro-spinal fluid, are subject to fluctuations. The trypanosomes appear and disappear, and, in the case of a patient proved to be suffering from the disease, may be absent at a given moment. The correlation normally existing between the penetration of the parasite into the cerebro-spinal fluid and the appearance of the nervous symptoms is sometimes wanting, or apparently so. The variations may also depend on the technique and skill of the observer; in certain cases diagnosis would be difficult without an examination of the blood, or even of the cerebro-spinal fluid, which is not always possible.

In every infectious disease, the first essential of therapeutics and prophylaxis is an early diagnosis: if the patient who has reached the somnolent phase be incurable, in the febrile stage it may be possible to treat and isolate him, and so to prevent the evil from extending. Credit is due to Greig and Gray for the introduction of a method of earlier diagnosis, by their discovery that in the enlarged lymphatic glands the trypanosomes are more constantly present and make their appearance earlier than in the cerebro-spinal fluid or in the blood. At the outset,

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[1] See the series of *Reports of the Sleeping Sickness Commission* (Royal Society).

the disease is a polyadenitis caused by the trypanosome: on making, with a needle fitted to a syringe, a simple, harmless puncture in the substance of the hypertrophied gland, a drop of fluid is obtained in which the parasites are at once visible by aid of the microscope. In the Kome and Sese Islands in Lake Victoria, Greig and Gray took the trouble to prepare a list of natives with enlarged glands; these people will be kept under observation, and in a few years their fate will be known.

The importance of gland puncture as a means of diagnosis is shown by statistics published by Dutton and Todd; in suspected individuals, the employment of this method resulted in trypanosomes being found in 97·2 per cent. of the cases, while the blood and cerebro-spinal fluid of the same individuals exhibited the parasites in only 54·2 and 59·6 per cent. The glands in the axilla, elbow, and groin yield results which are less constant, but still better than those furnished by the cerebro-spinal fluid and blood; this method by itself has rendered it possible to arrive at the proportion of those infected in a community, which, in many localities in Uganda, is from 70 to 90 per cent. Every subject whose glands are enlarged is affected with trypanosomiasis, and will develop sleeping sickness in due course; positive statements on this point are made by the natives themselves.

"In the Susu country, *bole* (hypertrophy of the glands in the neck) leads to *kikolo coundi* (sleeping sickness); in the Mandingo country, *kama courou* (*kama*, neck, and *courou*, glands) precedes *sinoro diankoro* (sleeping sickness); in the Foulah country, *leke* is soon followed by *madongol*, and at Sandonia sleeping sickness results from *koyona* (glands in the neck).

"Everywhere, in contaminated villages as in districts free from the disease, marabouts as well as headmen, *almamys* as well as husbandmen, said to me: 'Inflamed glands in the neck lead to sleeping sickness, and then death; they must therefore be removed as soon as possible in order not to be attacked by the disease'; and they do not hesitate to excise them. I have seen young people who had five or six, or even ten cicatrices as the result of this operation; a kind of damp dressing is applied for a few days, after which the gland is 'scraped out.' . . . The natives say that there are 'male glands and female glands,' the former of which remain solitary and

stationary, while the latter gradually increase in size and number."[1]

A disease affecting human beings can be experimented upon only when it is transmissible to animals, which is fortunately the case with regard to trypanosomiasis. Monkeys, with the exception of dog-faced baboons, can be infected with it ; and dogs, guinea-pigs, rabbits and rats—the animals regularly used in laboratories—as well as sheep, goats, and horses, are all susceptible ; mention is made of a hedgehog, which succumbed to the disease, and of a marmot, which died in a state of somnolence. Not all the features of the malady in human beings are reproduced in the experimental disease in animals ; the period of incubation, the gravity of the symptoms, and the result vary according to the species. Infected dogs are seen, which frisk about and are extremely lively ; and indeed in the human subject cases are on record in which, even at an advanced stage, patients have complained of insomnia. As is natural, it is in the monkey that the disease most resembles human trypanosomiasis, though it is comparatively seldom that a monkey develops typical sleeping sickness ; in this animal the trypanosomes remain in the blood, and do not often reach the brain. Harvey[2] has followed the entire course of the disease in a monkey, which, after being inoculated, remained quite well for seventeen months, without displaying any symptom other than emaciation ; in the eighteenth month the animal became weak, with slight paralysis of the hind-quarters and swelling of the lips and tip of the nose. Eccentricities in disposition then made their appearance, just as in the case of a human being ; the monkey became irritable, and the timbre of its voice altered ; death supervened in a state of coma. It is pitiful to see these poor creatures, no longer making faces or playing their customary tricks, but dull and with the mischievousness and sparkle gone out of their eyes, seated with their heads between their knees, in the usual attitude of monkeys asleep.

Sleeping sickness, which is an epidemic disease, like malaria, and is not contagious, is inoculated by the bite of a fly. It rarely happens that infectious maladies are transmitted by

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[1] Dr. Gustave Martin, *op. cit.*

[2] *Journal of the Royal Army Medical Corps*, May, 1905.

simple contact ; in order to pass from one subject to another, it is necessary for most kinds of virus to pass through an external medium ; the unknown microbe of small-pox and the tubercle bacillus are air-borne ; polluted water carries enteric fever and cholera, all germs are capable of being carried in the soil, and a wound contaminated with garden mould may result in tetanus. The link in the chain, however, instead of being inert, may be a living organism. An epidemic of plague is always an extension of an epizootic of the same disease among rats, since human beings are inoculated by the fleas that leave the fur of the dead rats ; malarial fever is transmitted by mosquitoes belonging to the genus *Anopheles* and its allies, which suck up the hæmatozoa from patients suffering from the disease, and then inoculate healthy individuals with them. In this case the mechanism is more complicated, since the mosquito, instead of being merely a simple carrier, is a *definitive host*, that is to say that the parasite passes through a regular cycle of transformations in the insect. A sojourn in the mosquito of at least a week is necessary to enable the hæmatozoon to assume a stage in which it is capable of infecting man ; the two media, man and mosquito, are therefore alternately indispensable to the species. Without the mosquito the reproduction of the malarial parasite would be impossible and the species would die out ; this is why the destruction of the *Anopheles* is equivalent to the abolition of malaria.

The transmission of sleeping sickness is more complex than that of plague, since the latter disease can be transmitted directly without fleas (through the respiratory passages, by means of sputum), while it appears that sleeping sickness can only be propagated by the agency of a particular fly. There are, however, fewer complications than in the case of malaria and mosquitoes, since up to the present it has not been proved that, within the body of the fly that harbours it, the trypanosome has to pass through a regular cycle of transformations, without which the species would become extinct.

It had already been proved, by means of Bruce's admirable experiments, that *nagana*, a disease of domestic animals, also caused by a trypanosome, is transmitted by the bite of an insect, one of the well-known *tsetse*-flies ; cattle cannot contract the disease through either drinking-water or herbage. The bite of

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a tsetse-fly is not poisonous like that of a venomous snake ; it has, on the contrary, a sucking and inoculating action, like that of a mosquito. The fly takes the trypanosome from one ox and inoculates another with it, and it is only by means of a tsetse-fly that the trypanosome of nagana can be transmitted. It was therefore reasonable to assume that the human trypanosome is conveyed from man to man by a fly, and for the last ten years naturalists have devoted much time and attention to the study of blood-sucking flies, especially tsetse-flies.

Under the name *tsetse* are included eight closely allied species, belonging to the genus of Diptera termed *Glossina*. The species by which nagana is transmitted is known to zoologists as *Glossina morsitans*, while sleeping sickness is conveyed by another species, called *Glossina palpalis ;* the *rôle* of the latter fly is placed beyond doubt by a whole series of proofs.

In the first place we have the geographical proof, afforded by maps which have been prepared showing the distribution of *Glossina palpalis* in Africa, and that of sleeping sickness. The two maps coincide, except that, as a rule, the zone of *G. palpalis* extends a little beyond that of sleeping sickness. In Uganda the coincidence is complete, and the proof is the more convincing owing to the fact that the two maps were prepared independently of each other ; the cases of sleeping sickness were marked down by doctors, and the biting flies were collected haphazard by natives and then determined by naturalists. The extension of the disease is therefore explained by the presence of the *Glossina ;* there is no sleeping sickness where *Glossina palpalis* does not occur, though there are countries infested with tsetse-flies where the disease is as yet unknown ; these regions are, however, "infectable," since the necessary condition is present. The recent appearance of sleeping sickness on the shores of Lake Mweru would not have occurred had the vicinity of the lake not been infested with tsetse-flies, and it is owing to the discovery of *G. palpalis* in Ukerewe that fears are now entertained on behalf of the population of that island.

Turning to proofs derived from observation, we find that the foci of the disease are situated along rivers, in wooded countries, and that *G. palpalis* frequents the shady banks of watercourses. The disease decimates families and villages, the members of which gain their living by fishing, while it

spares villages at a distance from water ; in the same village or family those who do not go to fish or to draw water escape, while those individuals who are occupied in catching and drying fish fall victims to the disease. As has been stated above, Koch mentions a family of which all the members who were engaged in fishing were attacked, with the exception of the mother, who remained at home. On the southern side of Lake Victoria the Wagada tribe, which occupied the shores of the Lake and prevented the other tribes from having access to it, in order to reserve the right of fishing, has been almost entirely destroyed by trypanosomiasis ; when the country was pacified other tribes engaged in fishing and were attacked by the disease. In the Missions cases are numerous among the male missionaries, who travel about and pass a considerable portion of their time in canoes, on the lakes and rivers, while the sisters, who lead much more sedentary lives, are not attacked.

In the peninsula of Buninga, where the latex of a liana (a species of *Landolphia*), which grows in the forest quite close to the waters of Lake Victoria, is collected for the preparation of india-rubber, almost all the natives employed in the work of collection fall victims to sleeping sickness. For a certain time, indeed, the work was at a standstill, since, in spite of the inducement of high pay, the negroes refused to undertake it. Labourers were then recruited in districts in which the natives were ignorant of the danger, and these in their turn paid tribute to the disease.[1]

Glossina palpalis is not fond of rocky banks, nor of those which are quite flat and where there are only grass, reeds, or papyrus swamps, nor does it like the shores of lakes where the virgin forest comes close down to the water, it loves spots where there is brushwood near the water, and where there are cormorants, herons, ibises, and even fishes, from which perhaps it derives the meal of fresh blood without which every two or three days it is bound to perish. When at rest, the fly sits at the edge of the water on the sand, stones, dead branches, or mangrove bushes, and it frequently happens that at a distance of a few yards there is scarcely a tsetse to be seen.

With regard to experimental proofs, the rôle of *G. palpalis*

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[1] R. Koch, *Deutsche medizinische Wochenschrift*, November 14, 1907.

in Nature has been reproduced by causing captive flies to bite an infected and a healthy animal alternately. In this way monkeys contracted the disease after an incubatory period of a fortnight, and flies which had fed upon natives suffering from sleeping sickness infected monkeys, which died in from three to five months. Other monkeys were infected by flies which had bitten patients forty-eight hours previously. The trypanosome, therefore, is capable of surviving for forty-eight hours in the digestive tract of the *Glossina*, and perhaps for a longer period, since monkeys have been infected by flies which had imbibed blood containing the parasites, not under experimental conditions, at an appointed moment and from a known patient, but while still at liberty and on a date which could not be determined. These experiments never succeeded with flies other than *Glossina*, but they have more than once been successful with species of tsetse other than *G. palpalis*. This fly is capable of transmitting other trypanosomes besides the parasite of sleeping sickness, and it is therefore natural to suppose that the human trypanosome can be transmitted by several species of *Glossina*.

Owing to their interest and importance to man, so much attention has been paid to tsetse-flies that their habits are fairly well known.[1] The different species of *Glossina* resemble one another very closely, and the lens and discrimination of the entomologist are needed to distinguish them. *Glossina palpalis*, which is a fly of small size, not very much larger than the house-fly, differs from the other species belonging to the same genus only in minute details of structure and coloration. A tsetse in the resting position is recognizable at once owing to the position of its wings, which, instead of being separated at the tips, as in the case of flies belonging to the genus *Stomoxys*, or each inclined at an angle with the inner edges in contact, as in the genus *Hæmatopota*, are closed flat one over the other like the blades of a pair of scissors. The colour of the body, which is some shade of brown or greyish-brown, the hue of the joints of the feet, and certain small structural details vary slightly according to the species. As a general rule tsetse-flies are

[1] See E. E. Austen, "A Monograph of the Tsetse-flies." (London, 1903. Printed by order of the Trustees of the British Museum.)

confined to damp, hot, low-lying localities, usually not far from water. It is rare for them to be met with on hills, although in Rhodesia *Glossina morsitans* has been observed at an altitude of some 4,500 ft. ; this, however, is highly exceptional. In some cases tsetse-flies are confined to "belts" of limited extent, dotted about over tracts of country otherwise free from them ; in other cases they are to be found more or less throughout a whole region, with the exception of the clearings, where they fortunately do not occur. It sometimes happens that they are to be found on one bank of a stream and not on the other, as was observed by Livingstone on the River Chobe.[1] Unlike the objectionable house-fly, they have no taste for excrement and other filth, and for this reason they usually avoid the vicinity of human habitations. According to Livingstone, this fact "has been observed and turned to account by some of the [native] doctors," who protect animals about to pass through a fly-belt by smearing them over with a mixture containing excrement and other ingredients. Foà states that, on killing an antelope in a patch of "fly," "in order to get rid of the tsetse, which literally cover game and hunters, it is only necessary to open the animal's belly and evacuate the entrails ; the insect at once ceases to torment you."

"On entering 'fly country,'" writes Bruce, "one is not left long in ignorance of the presence of the tsetse. The natives may be seen slapping their naked legs, the dogs bite round, and the horses kick."[2] According to Kirk : "In the morning while the dew hangs on the grass, and before the heat of the rising sun has warmed the air, the 'tsetse' is dull and sluggish, resting on the under side of some leaf or blade of grass ; when forced to take wing they may then be easily caught."[3] As soon, however, as the heat of the sun begins to make itself felt, tsetse-flies become most pertinacious in their attacks, dexterously

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[1] David Livingstone, "Missionary Travels and Researches in South Africa." (London : John Murray, 1857.)

[2] Surgeon-Major (now Colonel Sir) David Bruce, A.M.S., "Further Report on the Tsetse-fly Disease or Nagana in Zululand." (London : Harrison and Sons, 1897.)

[3] Dr. (now Sir) John Kirk : "On the 'Tsetse'-fly of Tropical Africa." (*Journal of the Linnean Society*, vol. viii., 1865, p. 149.)

avoiding a blow from the hand, and returning again to the very same spot. They are especially troublesome before sunset, but seldom bite by night, for which reason, when cattle have to be driven through a fly-belt, it is usual to do so at night. Yet this is not an infallible protection, and on fine moonlight nights travellers have often been bitten until towards midnight, when it begins to grow cold ; *Glossina fusca*, as well as *G. morsitans*, is known to bite at night. The flight of the tsetse-flies is rapid and straight ; they come to their prey from a long distance, doubtless guided by their sense of smell, since they are said always to fly up wind ; the rapid movement of the wings produces the high-pitched note, to which the popular name of these insects is due. In the early morning tsetse-flies often settle on men's backs in order to sun themselves, but when intent on feeding their procedure is different. Under such circumstances a tsetse-fly alights on the skin so gently as not to be felt, and for fifteen or twenty seconds it remains motionless, in a mistrustful attitude. When it believes itself safe it lowers its proboscis, separates its legs so as to get closer to its victim, and plunges the proboscis into the skin. A sharp prick is felt, but that is all ; in twenty or thirty seconds the insect's abdomen, which was previously empty and flat, becomes globular and red through being distended with blood. The tsetse is now not difficult to capture ; if driven off it is unable to fly for more than a few yards, and then settles in order to digest its meal.

The piercing organ or proboscis of a tsetse-fly is about 3 mm. in length, and, although by no means formidable in appearance, is actuated by a powerful musculature, and armed at the tip with a complicated arrangement of teeth, which serve to cut through the skin. Hides much thicker than human skin offer no resistance to it, and the rugged flanks of elephants were seen by Rankin streaming with blood from the attacks of these flies. Koch was informed by missionaries and natives that, on the shores of Lake Victoria, *Glossina palpalis* fed upon fishes lying at the surface, hippopotami, and crocodiles. With regard to the latter the Professor was sceptical, since the skin of these reptiles is protected by bony plates ; on shooting a crocodile, however, a swarm of tsetse was seen to descend upon the carcass. The flies insert their piercing organs

between the "scales" in the skin; further proof was afforded by finding in the stomachs of the flies nucleated crocodile blood corpuscles, and crocodile trypanosomes, which are distinct from the trypanosome of sleeping sickness. In consequence of this, Koch recommends the destruction of crocodiles as a useful prophylactic measure. Crocodiles deposit their eggs in particular spots, which are known to the natives, and to which they always return; rewards are to be offered in order to encourage the inhabitants to collect and bring in the reptiles' eggs.

Since there are animals which are susceptible to the human trypanosome, it would seem reasonable to look for it in the blood of the creatures, whether fishes, reptiles, birds, or mammals, among which *Glossina palpalis* lives. It is known that big game is the natural reservoir of the virus of nagana, which *G. morsitans* imbibes with the blood of antelopes and buffaloes, and that where the big game is destroyed the epizootic disappears.

What becomes of the trypanosomes in the stomach of the *Glossina?* Is the fly merely a living inoculating syringe, which plays a purely mechanical part, or do the parasites pass through in it certain necessary metamorphoses, termed by zoologists a *developmental cycle?* These questions can only be settled by experiments; the method of procedure consists in feeding captured flies on infected monkeys, and then, at regular intervals, making them bite healthy monkeys, and dissecting some of them. By this means it is possible to discover what becomes of the parasites in the fly's stomach, and whether, as in the case of malarial mosquitoes, a definite number of days must elapse before the bite becomes capable of conveying the infection.

Gray and Tulloch[1] observed a multiplication of the trypanosomes in the stomachs of only 1·47 per cent. of the flies that they used in experiments, and they did not succeed in infecting healthy monkeys with the new trypanosomes. The latter were parasites of the flies themselves, or "wild trypanosomes," which have no connection with sleeping sickness. In conjunction with

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[1] *Reports of the Sleeping Sickness Commission of the Royal Society.* No. 6, 1905.

Professor Minchin, Gray and Tulloch found that, during the forty-eight hours following a meal of infected blood, a certain multiplication of the trypanosomes takes place in the stomach of the *Glossina*.[1] After seventy-two hours, however, the process comes to an end; the trypanosomes commence to diminish in number, and finally disappear altogether. Although there is no periodicity in the infective power of the bite, as in the case of *Anopheles* and malaria, the *Glossina* nevertheless possesses peculiar properties as the vehicle of the parasite of sleeping sickness, since the trypanosome, which lives for only twenty-four hours in the stomach of flies belonging to the genus *Stomoxys*, survives for three days in that of *Glossina palpalis*.

While, therefore, there is no proof that the trypanosome passes through a developmental cycle in the tsetse-fly which is its intermediate host, it has not been proved that such a cycle does not exist. In this connection the most likely conclusion would seem to be that of Bruce, who states that development probably takes place, but he does not hesitate to assert that it will be found to be entirely different in character from such a metamorphosis as has hitherto been assumed, which is similar to what occurs in the case of the malarial parasite and the mosquito.

Although *G. palpalis* is the principal agent in the propagation of sleeping sickness, it has recently been pointed out by Koch that cases of the disease occur which cannot be attributed to the fly; and the French expedition which is carrying on investigations in the Congo has observed on its part certain facts which give ground for thinking that there is *something besides* the *Glossina*.

When the German expedition learnt that the disease had broken out at Kisiba, in the Bukoba country, to the west of Lake Victoria, search was made there for *G. palpalis*, but without success. Some of the patients had contracted the disease, not in their own country, but in Uganda, where they had stayed for varying periods; "foreign" sojourn could not, however, be accepted as an explanation in the case of fifteen women who had become infected without ever having left Kisiba, where *G. palpalis* does not occur. It was found on investigation that

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[1] *Proceedings of the Royal Society*, B, vol. lxxviii., 1906.

the women were married, and that their husbands were attacked with sleeping sickness, from which some of them had actually died. A native who had three wives had infected all three; the mode of transmission is not difficult to guess, and will, perhaps, be still more easily intelligible to those who are well acquainted with native habits. It follows that sleeping sickness may have a *conjugal* origin. The cases in question cannot be ascribed to the bites of other insects, since if blood-sucking insects other than *Glossina* were capable of inoculating the trypanosome, the disease among people who have never quitted their native land would not be found to be confined to married women, while unmarried females, children, old people, and women whose husbands are healthy, escape.[1] This new idea as to transmission constitutes a fresh point of resemblance between human trypanosomiasis and dourine, a trypanosomiasis of horses in North Africa, known locally as *mal du coït*, from the mode of contagion.

Supposing that a hundred or so sleeping sickness patients should reach Europe and be allowed to live as they chose, the disease would be transmitted as in Kisiba, and sleeping sickness would become established among us just as syphilis did in France in the fifteenth century.

Infectious diseases can be combated by several methods. Vaccination against anthrax and antidiphtheritic serum-therapy are types of the bacteriological treatment, in default of which measures of preventive hygiene, such as the prophylaxis of tuberculosis, are applied. Yet another method, chemical therapeutics—which is based on empiricism and has been adopted by modern chemistry—although the most ancient, is destined, perhaps, to become the latest; treatment by drugs, such as quinine in malarial fever and mercury in syphilis, is nowadays defined by regular formulæ, although the medicaments formerly used were of a more or less mysterious nature.

It remains to be seen whether we shall soon be in possession of a vaccine, serum, or chemical remedy for sleeping sickness, but the institution of a system of prophylaxis has been commenced without waiting for the completion of the scientific investigations. The campaign against malaria forms

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[1] R. Koch, *Deutsche medizinische Wochenschrift*, November 14, 1907.

an admirable model, and it would be impossible to find a better programme than the instructions drawn up for the Congo expedition.

Unfortunately no means of attacking the tsetse, on the lines of the measures adopted against malarial mosquitoes, have yet been discovered. Mosquito larvæ live in stagnant water and breathe atmospheric air, with which their respiratory apertures are in communication when the larvæ float suspended from the surface film ; if a small quantity of petroleum be poured upon the pool a thin superficial layer of oil is formed, by which the larvæ are asphyxiated. Tsetse-flies, however, do not lay eggs, but are viviparous, producing at each birth a single annulate larva which, after crawling away into a suitable hiding-place, becomes transformed into a kind of rigid sac or *pupa*, from which the perfect insect emerges after an interval of six weeks. Since the pupæ are not found in definite spots, it is not easy to attack them, but the measure that corresponds most closely to the draining of pools for the destruction of malarial mosquitoes consists in burning the brushwood round inhabited centres. The fire destroys the pupæ and abolishes the shelter necessary for the existence of the flies ; the German expedition recently lived in perfect security in the centre of burnt clearings.

During the year 1906, on the advice of Professor Koch, Sigawanda Island, in Lake Victoria, near Muanza, where tsetse-flies were plentiful, was denuded of trees and bush with the exception of a small valley and a particular spot on the shore. *Glossina palpalis* disappeared completely from the denuded area, but continued to exist elsewhere. On the shores of the lake denudation is not an expensive operation ; the steamers consume large quantities of wood, the sale of which defrays the cost of the undertaking.

If the blood of big game were a living reservoir of the virus of human trypanosomiasis, as it is of that of nagana, it would be necessary to advise that the game should be ruthlessly destroyed. In reality, however, the reservoir of the virus is the negro, and we cannot exterminate him in order to preserve him from the disease.

Not much is to be hoped for from the ingenious suggestions of Monticelli, who advises the utilization against mosquitoes

and flies of their natural enemies, such as spiders and other insectivorous creatures. The measures to be adopted must deal with human beings.

Since trypanosomiasis is spread by the movements of populations, these must be regulated and rendered harmless. All such measures are reducible to two: the prevention of migrations from infected centres into healthy ones, and the prevention of penetration into infected centres on the part of healthy individuals, who might become infected and carry the virus into regions previously free from the disease. The exchanges of soldiers and labourers should take place only between healthy or contaminated zones. Prophylaxis requires the preparation of good maps of the disease, and this medical geography is one of the great tasks of the French expedition.

"The measures recommended are briefly: (1) The establishment of medical posts of inspection along the trade routes leading from infected to uninfected districts; and (2) the removal of infected persons from posts in uninfected districts to places already infected. . . . As an example of the applicability of the proposed measures, consider the case of Nyassaland. It is certain that the natives of the southern as well as the northern shores of Lake Tanganyika will shortly be very heavily infected with trypanosomiasis. Labourers are engaged from the neighbourhood of Tanganyika to work in Nyassaland. There is constant communication between these two districts, since one of the most important caravan routes to Central Africa runs between Lake Nyassa and Lake Tanganyika. . . . It is evident that the communication between these two areas should be stringently controlled. Posts of inspection should be established to prevent infected porters in caravans, or labourers, from entering British territory. Every employer of labour must be made to understand the danger of enlarged neck glands, and should be instructed to send negroes possessing them to the nearest post of inspection. Each person residing or travelling in uninfected areas must be made personally responsible for the presence of persons with enlarged glands in his following. It is believed that the difficulties in applying these measures will not be as great as might be anticipated. Natives will soon learn and appreciate the danger of enlarged glands; they have long recognized their

significance in Sierra Leone, Uganda, and in parts of the Congo Free State. It will admittedly be impossible altogether to control the movements of individuals, but it is not from single persons as a rule, travelling only a few miles, that danger is to be apprehended. It is organized transport of groups of negroes which is dangerous."[1]

At the French Colonial Congress of 1904 an experiment in prophylaxis was proposed by the Anti-Slavery Society of France. The idea was to select a village in which sleeping sickness was known to exist, and to transport the inhabitants to a locality where tsetse-flies did not occur ; the result would be that the only people in whom the sickness would appear would be those already attacked at the time of the removal, and since the disease is not hereditary it would die out ; the example set would be followed by other villages. Instructions are to be drawn up for the benefit of Europeans resident in the Congo,[2] who will learn to protect themselves against tsetse-flies. The picture postcard, a graphic and expressive means of imparting instruction, has already been employed in order to popularize the rules of prophylaxis.

Vaccination and serum-therapy cannot be expected to be of much avail in human trypanosomiasis. Therapeutic serums are furnished by animals which are susceptible to a disease and have been rendered immune to it ; it has been proved that in no case does the serum of an animal, which is sensible to a trypanosome and has been immunized against it, exert any curative effect on the disease experimentally produced on other animals.

The attempt has been made to treat sleeping sickness, as also the trypanosomiases of animals, which are more accessible

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[1] John L. Todd, "A Means of Checking the Spread of Sleeping Sickness," *Lancet*, July 7, 1906.

[2] "For the sites of houses localities should be chosen at a distance from damp and marshy spots where tsetse-flies abound, and also from huts containing natives suffering from sleeping sickness. Flies should be prevented from entering houses by means of wire-gauze, or if this be impossible, one should work or sleep in a room thus protected, or under a mosquito-net. In the bush, and especially on rivers, on board steamers or in canoes, wear high boots, and protect the head and neck by means of a mosquito-veil ; wear gloves to guard the hands and wrists ; clothes should be loose enough to prevent the tsetse's proboscis from reaching the skin" (Laveran).

to experiment, such as nagana, by means of virus which has been attenuated (either by age, or by the action of heat, or by passages through different species of animals), with a view to producing the benign disease that confers immunity to the malignant type. The results are disappointing ; the attenuation of the virus merely results in a longer period of incubation, and the disease, once it has declared itself, follows its normal course.

There is, therefore, neither vaccine nor serum, and the future rests with chemical therapeutics. The problem is to find in the case of sleeping sickness a drug as potent as quinine or mercury in other diseases. The initiative came from Lingard, who, in India some ten years ago, attempted to treat *surra* in horses with all kinds of chemical products ; alkaloids of cinchona, phenic acid, iodoform, iodine, iodide of potassium, iodide of potassium and mercury. The enumeration of these drugs, all of which proved useless, suggests that Lingard was influenced by the treatment of malaria and syphilis. The only thing that yielded favourable results was arsenic in the form of arsenious acid, cacodylate of soda, or Fowler's solution. Lingard's finding was confirmed by Bruce, and adopted by Laveran and Mesnil for the treatment of nagana ; from this time forward arsenic occupied an important position in the tropical pharmacopœia.

Arsenious acid destroys the human trypanosome in blood drawn off into a test-tube ; when injected subcutaneously or intravenously into infected animals, it causes the parasites to disappear from the general circulation, at least temporarily. Laveran has recommended the early treatment of human trypanosomiasis by means of strong doses of arsenious acid, administered at intervals, in the hope of destroying the microbes before they penetrate into the nervous centres, where they give rise to the characteristic symptoms of sleeping sickness.

Professor Ehrlich, the eminent German scientist, and his Japanese collaborator Shiga, encouraged by the properties of arsenious acid and quinine, made experiments on trypanosomiases with all kinds of products of organic chemistry. After hundreds of fruitless attempts they obtained good results with a compound which is both a remedy and a stain ; the substance in question is a dye belonging to the benzopurpurine series,

upon which they bestowed the name trypanred (*Trypanroth*). When injected experimentally into mice, it dyes the animals a most beautiful red, and mice so treated have incarnadine feet, tails, and ears protruding from their white fur ; the colour can be mixed with cakes given to the mice for food. The staining property of the drug, which would not act did it not impregnate the tissues, serves to accentuate and render perceptible the novel fact of "coal-tar colours" being received into the pharmacopœia, just as were formerly quinine, antipyrin, and the substitutes for the latter.

Neither arsenious acid nor trypanred, however, has a sovereign effect upon the human trypanosome, and the new therapeutics has sought to make progress in three different ways.

At the Pasteur Institute in Paris, Laveran showed that by associating several drugs together, and administering suitable doses of each in turn, their efficacy is increased. When monkeys inoculated with sleeping sickness were treated with arsenious acid in conjunction with trypanred, as proposed by Laveran, the parasites disappeared from the blood and never returned.[2]

Dr. H. Wolferstan Thomas, of the Liverpool School of Tropical Medicine, successfully employed an arsenical compound containing 38 per cent. of arsenic, and forty times less toxic than arsenious acid ; the arsenic compound in question is a white powder belonging to the meta-aniline group, and is now well known under the name *atoxyl*.[3] This drug does not cause renal lesions, as trypanred sometimes does ; it can be inoculated either subcutaneously or intravenously, and can be employed in conjunction with Ehrlich's trypanred and other drugs. On being administered to man, it was found that atoxyl causes the trypanosomes to disappear from the blood, but that they persist in the cerebro-spinal fluid, perhaps because the meninges do not permit the drug to pass through.

At the Pasteur Institute Mesnil and Nicolle,[4] while elucidat-

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[1] *Berliner klinische Wochenschrift*, March 28 and April 4, 1904.

[2] Communications made to the French Academy of Sciences, 1904-5.

[3] *British Medical Journal*, May 27, 1905 ; Mesnil and Nicolle were studying this substance when Thomas's paper appeared. Since about 1902 atoxyl has been used in the treatment of anæmia and various nervous disorders.

[4] "Traitement des Trypanosomiases par les Couleurs de Benzidine," *Annales de l'Institut Pasteur*, 1906.

ing the chemical theory of the action of the "coal-tar colours," endeavoured to discover colour-medicaments superior to trypanred, a substance which does not occupy an isolated position in chemistry, but has allies among the series of colours termed "benzidine colours." This is a group, the members of which differ only in certain constituent parts of their molecules. The related molecules possess in common a principal atomic nucleus, upon which are grafted secondary groups of atoms; each of these groups possesses a certain property, chemical or therapeutic as the case may be. If, by means of particular reactions, we cause the molecular structure to vary, by substituting one definite atomic group for another, we at the same time cause the properties of the compound to vary, and the influence of the molecular structure on the therapeutic properties can be ascertained by experiment. We can fabricate as many of these "multivalent" bodies as we choose, and can arrange the substitutions so as to produce the highest possible therapeutic efficacy. Mesnil and Nicolle succeeded in determining the molecular structure upon which the destructive effect towards trypanosomes depends, and among the benzidine colours produced under their direction were some which appeared to them to be of value in the treatment of animal trypanosomiasis; some of these which are superior to trypanred, when administered experimentally to monkeys infected with the human trypanosome, caused the parasites, in cases in which the disease normally develops in one or two months, to disappear from the circulation for a period of about thirty days; when the parasites reappeared, a repetition of the treatment produced the same effect. A remedy which occasions the prolonged disappearance of the trypanosomes from the blood is a powerful ally in the prophylaxis of sleeping sickness.

As the result of their comparative researches upon these medicaments, Mesnil, Nicolle, and Aubert conclude that the best remedy for human trypanosomiasis is atoxyl, employed either alone or alternately with one of their colours—a violet dye.

Professor Koch tried the effect of atoxyl upon the infected population of the Sese Islands in Lake Victoria. At the outset he gave a subcutaneous injection of 50 centigrammes on two successive days, and found that between the sixth and the

eighth hour after the injection the parasites disappeared from the blood and enlarged glands, and were not seen again for some ten days, after which the injections were repeated. There is no difficulty in giving this double injection for four or six months, at intervals of six days. The general condition of the patients improved under the treatment, and Koch soon had a thousand negroes who were anxious to receive the injections; his first impressions as to the efficacy of atoxyl were highly favourable.[1]

In order to be able to form a positive opinion, it is necessary that the patients who have undergone the treatment shall be kept under observation for a year or more, since trials upon animals have invariably shown that an initial success is followed by relapses. Koch will make no pronouncement as to the therapeutic value of atoxyl until he has observed the relapses and their subsequent progress. Observations of this kind are being made in Europe upon white patients, among others by Dr. Louis Martin at the hospital attached to the Pasteur Institute in Paris.[2] The prophylactic utility of atoxyl is already beyond doubt, since the decrease of the epidemic is ensured by ridding the blood from the trypanosomes, which *Glossina palpalis* might otherwise disseminate.

Interesting analogies are established by the foregoing facts between three diseases, caused by pathogenic organisms which are now known. We refer to malaria, syphilis, and trypanosomiasis, which are influenced respectively by quinine, mercury, and atoxyl; all three are subject to relapses and, after the subacute initial phase, assume a chronic type. The parasites on being driven from the circulation are not always totally destroyed, since they may one day return to the attack; they take refuge in other tissues, such as the spleen or marrow of the bones, or retire into cells the whereabouts of which are more or less unknown. They lie dormant for weeks, months, or years, until the efficacy of the drug is exhausted or the resistance of the organism becomes diminished, when they again begin to multiply and to circulate, it may be with their

[1] R. Koch—letters of June 10, October 15, and November 5, 1906, published in part in the *Deutsche medizinische Wochenschrift*, supplements to the issues of December 20, 1906, and January 10, 1907.

[1] *Annales de l'Institut Pasteur*, t. xxi., March, 1907.

vigour attenuated, and the fire is rekindled from the embers. Each outburst of the infection must be met by a specific treatment.

After vaccination for smallpox and anthrax, immunity is practically absolute, and the organism is for a long time refractory to doses of virus much stronger than those by which it is liable to be attacked under natural conditions. There are infectious diseases, caused by lower animals or Protozoa, from which the animal recovers, but nevertheless retains living parasites in its system. To the carrier itself these retained parasites are no longer pathogenic, though they may be so to other individuals which have not been rendered immune; thus if a healthy animal be inoculated with blood from one which has been "cured," the former contracts the disease. This is the case with regard to the cattle disease known as Texas fever. Other infections are also characterized by recovery and retention of a few microbes, but the recovery is merely provisional, and the microbes that have survived continue to be pathogenic to their host; this is what happens in the case of syphilis and diseases caused by trypanosomes, and these maladies have made us acquainted with new forms of immunity and sensibility.

From the numerous experiments in chromotherapy, that have been made upon various trypanosome infections, Professor P. Ehrlich has deduced two general concepts, which are also true with regard to sleeping sickness. These ideas are opposed to one another, although not perhaps contradictory.

On the one hand, in these relapsing diseases, the condition of the organism between two relapses does not remain the same, and it has been shown by means of very delicate methods that it acquires a certain degree of very real immunity. *The parasite becomes more and more sensible to the action of the drug*, and a fresh relapse is cured more easily than the previous one. We are led, remarks Ehrlich, to conclude that, "in consequence of the absorption of the trypanosomes killed by the atoxyl, the organism acquires a degree of immunity which no longer permits the normal development of the parasites." Yet, seeing that a few parasites still remain alive, it is very difficult to believe that the cure is complete.

On the other hand, in certain cases it is observed that, in the

interval between one relapse and the next, the activity of the drug becomes weakened. In such cases, according to Ehrlich, it is the parasite and not the organism that has undergone a change.

The proof of this is that if a fresh animal be inoculated with the parasite, it receives much less benefit from the same treatment than an animal inoculated with parasites which have never been subjected to the action of the drug. *The parasite therefore becomes more and more resistant to the action of the remedy.* Ehrlich observed and even produced races of trypanosomes resistant to trypanred, to the blue colour of Mesnil and Nicolle, and to fuchsin ; in the case of certain sleeping sickness patients it would therefore be possible for the treatment to result in the production of races of trypanosomes resistant to atoxyl.[1] On the one hand, the organism becomes immune to the microbe, while on the other the microbe becomes immune to the organism. Doubtless the fact is of general occurrence in infections, but one of the two phenomena is usually concealed by the other.

Habituation to drugs is a fact of which medical men have long been aware. In the treatment of syphilis they noticed that certain patients *become accustomed* to mercury, which after a time ceases to exert its full effect upon them ; it was for this reason that clinicians, such as A. Fournier, long ago advised that mercurial preparations should be varied in order to overcome the difficulty : they had thus discovered the law at which we have lately arrived by means of experimental research.

In the case of sleeping sickness as in that of syphilis, the future therefore belongs to what Erhlich terms *combined* treatment, or, more precisely, to *alternating* treatment, as it had previously been described by Laveran. The physician must be careful not to use up his remedies, and should always have one in reserve. In syphilis he will take good care not to give both atoxyl and mercury at the same time ; but, to a patient upon whom mercury appears to be losing its effect, he will administer axtoyl as a substitute and will afterwards again have recourse to

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[1] The resistant *race* is indeed the right term to use : the race thus created is perpetuated, in the case of the parasites, from generation to generation, and, in that of the inoculated animals, from passage to passage. This, according to Ehrlich, is a new instance of the transmission of acquired characters.

mercury. In the case of sleeping sickness, another drug may sometimes be used instead of atoxyl, but where possible it is preferable to avoid the conditions favourable to the immunization of the microbe and the formation of a resistant race of parasites. The rule suggested by experience and common sense is to strike hard with the most powerful remedy at the commencement of the treatment, so as to ensure that the patient's first recovery shall be as rapid and as thorough as possible.

If a resistant trypanosome loses its resistance in passing through the tsetse-fly, its intermediate host, the matter is not so serious as it might be, since the resistant race will die out with the patient in whom it occurs. On the other hand, if the resistant trypanosome should retain its character, even after passing through the fly, the resistant race would become permanently established and might be met with in all the patients in a given region, so that treatment would encounter fresh difficulties.

The influence of the living disseminator or intermediate host on the virulence of the microbes harboured by it has been studied in another instance. Marchoux and Salimbeni have observed in Brazil an epidemic disease of fowls caused by a *spirillum*: just as the trypanosome of sleeping sickness is inoculated by a tsetse-fly, so the fowl spirillum is carried by a tick known as *Argas miniatus*. The virulence of the spirillum is somewhat unstable, but is in no way modified as the result of a sojourn in the body of the *Argas*, which on the contrary fixes it, so that it is passed on by the tick in exactly the same degree as that in which it was received. "In passing distinctly from fowl to fowl, the spirillum gradually loses the power of causing the death of the animals into which it is injected. On keeping it for some time in capuchins and other pigeons, it adapts itself to the species in which it is cultivated, and becomes incapable of infecting the fowl; similarly, when passed through chicks it very soon ceases to be pathogenic to any except young birds. Under natural conditions, however, it retains its virulence, since, in countries in which fowl spirillosis occurs, poultry farms are constantly ravaged by the disease. The maintenance of the virulence is evidently due to *Argas miniatus*, which serves as the intermediate host of the fowl spirillum. Experiments prove this, but they also show that the

ticks cannot revive the lost virulence. When kept at a temperature of 28° to 29° C. (82° to 84° F.) they are capable of transmitting indefinitely a disease which is constantly identical with that of the animal from which they obtained the virus."[1]

The future will show whether the treatment of sleeping sickness creates races of trypanosomes resistant to atoxyl. The problem is a grave one, not only for therapeutics but also for epidemiological hygiene.

The discovery of atoxyl cannot therefore be considered as the conclusion of therapeutic research ; the treatment must be perfected, and we must not rest satisfied until we possess several efficient remedies.

At the time of writing, the French expedition to the Congo is pursuing its investigations and the German expedition has just returned to Europe. For full information we must await the detailed report that is to be published by the latter ; but in the meantime intelligence, which will form a provisional conclusion to this chapter, is to be found in certain letters from Professor Koch.[2]

The action of atoxyl in sleeping sickness is beginning to be better understood. After a few weeks of treatment the enlarged glands diminish in size, and trypanosomes are soon no longer to be found in them ; the parasites finally even disappear from the blood. If the injections be stopped eleven days (at least) after the interruption, the parasites may again be found in the glands ; from the twentieth day onwards they are met with again in 25 per cent. of the patients examined under these conditions ; then they disappear once more, and about the sixtieth day are no longer to be found. The question arises whether there is merely a local glandular immunity which does not extend to the other tissues. In any case the cure of the glands does not entail the definitive cure of the patient. The trypansomes may reappear in the blood, and we then have a relapse ; but if there are cases of relapse, it is not an absolute rule.

[1] E. Marchoux, "Instabilité de la Virulence des Spirilles et sa Fixation par l'Hôte invertébré," *Comptes rendus de la Société de Biologie*, October 12, 1907.

[2] Written from the Sese Islands, on April 25 and September 5, 1907; published in the *Deutsche medizinische Wochenschrift* of November 14, while the French edition of this book was in the press.

The results of his method are announced by Koch in the following terms :—So long as the patient remains under treatment the trypanosomes do not reappear in the blood ; the treatment has been continued for ten months (the period covered by the observations made up to the present time). Thus, for ten months the patient, having no parasites in his blood, will not provide tsetse-flies with them, and so will not contribute to the spread of the disease.

The prophylactic efficacy of atoxyl is not its only merit. In many instances its use results in the definitive (in so far as it is permissible to employ the term at present) disappearance of the trypansomes, and the earlier and more regular the treatment has been the more certain is the result. In slight cases recovery appears to be the rule after treatment lasting from four to six months ; in severe cases successes are also observed, but there are some relapses.

Here are a few statistics. At Bumangi, in a mission-station which permanently accommodates 20 patients, there were 212 deaths in four years, or if we reduce the figures to 100 patients and one year, 265 deaths. At Kisubi, with accommodation for 80 patients, there were 687 deaths, or 214 deaths per year and 100 patients. This high rate of mortality is explained by the fact that the natives sought admission when they were already ill and had only four or five months to live. Almost all these patients are dead.

On the other hand, out of 1,633 subjects treated, 131, or 8 per cent., have died in ten months ; no doubt there are slight cases among this number, and if we only consider the serious cases we find that there were 78 deaths among 374 patients, or 22·9 per cent. Again we must deduct the patients who have not submitted to the injections with sufficient regularity. In short, according to Koch, the mortality among the natives treated is from a tenth to a twentieth of the rate among the non-treated.

It is not an easy matter to treat natives. The injections are painful, and they do not like them ; since they are not under any kind of compulsion they go away, either after the first injection, or when they feel better, or when a recovery, which it is too soon to consider permanent, is noticed ; when once more attacked by the disease they return. The doctors have

to exercise much patience and activity in order to collect a sufficient number of continuous observations.

The trypanosomes have never become refractory to the action of atoxyl, and Koch has not observed any facts in confirmation of the fears that might be suggested by Ehrlich's admirable experiments; his practice has not resulted in the production of *races resistant* to the drug.

Overdoses of atoxyl sometimes produced blindness in those to whom they had been administered, without any lesion of the eye or optic nerve being discoverable with the ophthalmoscope; normal doses never gave rise to this complication. In Koch's treatment the normal dose is 50 centigrammes; it is given on two successive days, and the double injection is repeated at intervals of ten days. Although the injections are painful, they cannot be dispensed with; the "normal" dose, administered by the mouth, does not produce the desired effect, and a stronger dose, like a too strong injection, entails the risk of toxic complications.

The prophylactic campaign has been organized by Koch according to rules, of which some had already been suggested by the travellers and scientists who preceded him, while the remainder were the result of his own observations. These rules are as follows: Establish stations for patients. Employ persuasion in order to attract the natives, who do not come of their own accord, especially in the first stage of the disease. Treat patients with atoxyl, or with another drug when something better has been discovered. Allow only those patients to be discharged whose blood is free from trypanosomes. Prevent the exchanges of natives, and especially of patients between infected and uninfected districts. When a tsetse-fly area is sparsely populated, transport the inhabitants to a region in which *Glossina* does not occur.—Assuming all patients suffering from trypanosomiasis to have been removed from a district, it remains for future investigations to show how long a period of time must elapse before the local tsetse-flies cease to contain trypanosomes; in Koch's opinion, however, the necessary interval may possibly be one or two years.—Clear the ground, especially at the water's edge, around villages, at the places to which natives go to draw water, at landing-places for canoes, and on the banks of rivers where there is most traffic. Lastly, destroy crocodiles.

The results obtained by Koch are encouraging, but we believe that the French expedition to the Congo has less faith than the German professor in the efficacy of atoxyl.

In the case of sleeping sickness, as in that of malaria and syphilis, if drugs cannot cure the infection at the outset, they are henceforth capable of promoting the evolution of an acute and fatal malady into a chronic, latent, and tolerated disease.

The evolution of acute into chronic diseases appears to be a fact of general occurrence in pathology. We see it take place in the individual, and it must have come to pass in the course of centuries in generations of human beings. Tuberculosis and leprosy were without doubt originally acute infections, which have ended by making a compact with humanity. They live, as it were, in a state of armed peace with our cells, but their evolution is not complete; they destroy the individual, but in the end the species will perhaps destroy them.

ENTERITIS AND INTESTINAL MICROBES.

Appendicitis is in no danger of being forgotten at the present time, and on all sides a great deal is heard of enteritis, these two maladies being equally subjects of general conversation. Who at dinner has not found himself seated between the guest whose entire family has been operated upon, or is in a fair way of being so, and a charming woman, the slave of a regimen, who, by courtesy of the hostess, receives special dishes, averts her eyes with horror from all animal food, swallows a pile of starchy food with conviction and, on rising from the table, only regrets that she is unable to go and lie down on her couch? A modern dinner is indeed the best place at which to obtain information on the subject of lactic ferments and medicinal broths. One might easily smile at all this, and say with Molière or La Bruyère: "So long as mankind is mortal and yearns to live, the doctor will be sneered at and well paid." It is, however, something more than a fad, since everyone is interested in questions of general hygiene and diet, and the Guild of Æsculapius, no longer confined to the temple sanctuary, now includes half the public. At the same time the professional practitioner will always have sufficient to do; for the instructed curiosity of the public has never acted to the detriment of the real artist.

Four centuries have gone by since Ponocrates and Gargantua "sat down to table and began merrily to converse, discussing the virtue, efficacy, and nature of everything that was served to them: bread, wine, water, salt, various kinds of meat, fish, fruit, herbs, and roots, and the preparation of the same. So well and so thoroughly did what was said remain in the memory, that at the time there was no doctor who knew half so much. . . ."

Wags and sceptics would have us believe that enteritis is a kind of nervous disease of the stomach, which is treated in Paris by swallowing certain medicinal broths, or by going to

Switzerland to eat cereal foods. As a matter of fact, however, it is an all too common intestinal malady, the existence of which imposes the necessity of learning to be careful in the selection of food.

Every disease has a history of its own, which commences when the malady is described and classified by clinical medicine, as a botanist describes and classifies plants. The causes of the disease and the laws by which it is governed are then gradually discovered, and it passes from the clinical domain into that of science. A process of evolution of this kind has been seen in the case of anthrax, as the result of the observations of Davaine and the genius of Pasteur, and in that of diphtheria owing to the discoveries of Roux and von Behring: Pasteurian vaccinations and serum-therapy have become types of scientific therapeutics. It is but a few years since enteritis was still in the clinical stage, but the work of Metchnikoff and his pupils places it upon a scientific basis, and creates for it a new therapeutic system.

Enteritis is a zymotic disease of the intestine, though not a specific malady like anthrax and diphtheria. It is due, not to a microbe possessing definite properties, but to legions of microbes belonging to the most widely different species, which cause fermentation and putrefaction. In the small intestine, where few or no microbes are found, take place the useful fermentations which are caused by the digestive juices of the mucous membrane and pancreas: in the large intestine, on the other hand, microbes swarm in such enormous masses as to constitute a good third of the contents. What purpose do they serve, seeing that by the time that food has arrived at this point useful digestion has been accomplished? These organisms flourish here on their own account, like weeds, effecting the decomposition of the waste food-materials without benefit to nutrition. They produce substances which irritate the mucous membrane and are toxic to the organism; these become diffused in minimal doses, take effect in the long run, and impair, without destroying, the higher cells of the nervous system and glands; the chronic trouble thus caused is known as—old age.

There can be no *single* remedy, whether vaccine or serum, of any avail against microbes which pass away and are renewed in masses, so that their actions are confusedly intermingled;

or against poisons which, instead of, like tetanus or the bite of a venomous snake, attacking the system with sudden intoxication, act by the aggregation of infinitely small effects. The problem is to prevent the occurrence of harmful fermentation and putrefaction in the intestine, and so to suppress the poisons at their source. Metchnikoff has endowed medicine with a new method of treatment, by showing that the species of microbes that swarm in the intestine are subject to the great law of vital competition ; that their antagonisms provide us with the means of intervening, of attacking one kind by the aid of another, of splitting up masses in order to acquire the control ; and that science is capable of substituting for the prevailing disorder a system of rational selection. The result is a therapeutic method based upon the laws of the struggle for existence and natural selection.[1]

All intestinal inflammation, especially that of the large intestine, is included under the generic term enteritis, which is therefore applied to several distinct diseases. Enteric fever and cholera are examples of hyper-acute enteritis, while dysentery is an epidemic form, caused either by the bacillus discovered by Chantemesse and Widal (usually dysentery of temperate climates), or by an amœba (as is generally the case in tropical dysentery) : dysentery due to bacilli can be treated by a serum prepared at the Pasteur Institute by Vaillard and Dopter. The tuberculous form of enteritis results when the intestinal mucous membrane becomes the seat either of primary tubercle or of secondary invasions. There are many other kinds of diarrhœic enteritis in addition to the foregoing : in one instance the patient may have just returned from a hot climate ; in another, the intestine has perhaps been injured by medicines too strong for it ; or again, it may be a case of a *bon vivant*, who has overtaxed and impaired his mucous membrane, and will have to submit to a regimen in order to be cured.

The usual form of enteritis that people talk about, however, is neither dysentery nor intestinal tuberculosis nor tropical

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[1] E. Metchnikoff, "Études sur la nature humaine," 1903, chapter x. "Essais optimistes," 1907, part iv. "L'Hygiène des intestines" (a lecture delivered in 1906 at the Institute of Hygiene in London) ; *Revue générale des sciences*, October 30, 1906.

diarrhœa, but muco-membranous enteritis or entero-colitis. It is acute or chronic, and is accompanied by either diarrhœa or constipation ; the two forms are not independent of one another, since chronic muco-membranous enteritis is usually the result of an attack of the acute diarrhœic type.

The intestinal mucous membrane is pitted with a multitude of little glands, which in the large intestine are chiefly mucus glands. Mucus is the saliva of the intestine, the slimy secretion which moistens the mass of ingested food, and is produced throughout the entire intestinal tract. If absorption be the special function of the small intestine, the large intestine is also capable of absorbing various products of digestion. It absorbs both medicines and poisons fairly well, and also has a sensitiveness of its own, since it is richly supplied with nerve fibrils, which are controlled by the sympathetic system. In enteritis all these functions are disordered, and the accompanying pain is the result of inflammation. Patients void, in the form of glair or "membranes," abnormal quantities of mucus, either because the latter is secreted in excess or because it does not dissolve when digestion is complete, as it does under normal conditions. Digestion is vitiated by the putrefactive processes.

In enteritis the nerves are often so largely concerned as to have led to the belief that it is a nervous disease. Gouty people, and those who are overworked, low-spirited, or in a nervous condition, are especially liable to it. It is accompanied by neuropathic troubles, palpitation, asthma, neuralgia, melancholia, and the other concomitants of neurasthenia. Neurotic patients are sometimes seized with attacks of pain so similar to those in typical enteritis that the condition has been termed muco-membranous entero-neurosis. The symptoms, however, are less constant and less well-marked than those of true enteritis, so that the patient might sometimes be thought to be suffering from hepatic colic, or else from an attack of hysteria. It is not enteritis, because there is no lesion of the intestinal mucous membrane ; the case is one of neurosis, the treatment for which consists in isolation, the rest-cure, "feeding up," and psycho-therapy.

Enteritis does not originate in the nerves, but it is in the nerves that its effects are seen, since nervous and arthritic

subjects are especially liable to the disease. Definitions of arthritis differ widely, but there is general agreement as to something which is common to the victims of neuralgia and migraine, the asthmatic, and the ultra-civilized, all of whom are dwellers in towns and eaters of meat; this is a predisposition which must exist before an intestinal infection can degenerate into chronic muco-membranous colitis.

Everything that facilitates intestinal putrefaction promotes enteritis, and everything that diminishes the "motivity" of the intestine promotes putrefaction, since stagnant food-materials form an admirable culture medium. Now, the intestine performs its functions badly when the abdominal organs are out of order, and the doctor must make an examination of the stomach, liver, and kidneys, in order to discover the secondary causes of enteritis, which are sometimes determining causes. In an intestine which has become sluggish through sympathy with some other organ, stagnation prepares the way for putrefaction; the products of putrefaction irritate in their turn the mucous membrane, muscles, and nerves, and the general state of things becomes worse and worse. It is a short circuit of causes and effects in which it may be difficult to distinguish the primary cause. Moreover, the student of enteritis will inevitably be confronted with the serious question of its relation to appendicitis, which, some three years ago, was the subject of a lively debate at the French Academy of Medicine. Professor Dieulafoy, the champion of prompt intervention in the case of pronounced appendicitis, complained that too many operations were unnecessarily performed on patients suffering only from enteritis. The thesis of his communication of May 29, 1906, sounded the alarm: "A number of people whose ailment is merely muco-membranous typhlo-colitis, are wrongly operated upon for appendicitis which is non-existent." Such patients complain of pain which is most marked in the right iliac fossa; the appendix is removed and found to be healthy, while the typhlo-colitis shows no improvement. The sufferers go elsewhere for treatment, and may be met with at Plombières or Châtel-Guyon, carrying with them, inscribed upon their bodies in indelible characters, the record of an error in diagnosis. Cases in which entero-colitis leads to appendicitis are exceptional, nay "extremely rare"; let us

therefore beware of operations, and temper the surgical with the medical spirit. "While," remarked Dieulafoy, "I am an absolute believer in intervention in appendicitis, I just as emphatically disapprove of it in the immense majority of cases of typhlo-colitis (enteritis of the colon and cæcum), in which appendicitis does not exist." In the discussion that subsequently took place at the Academy, surgeons such as Reclus and Richelot mentioned instances of the co-existence of enteritis and appendicitis. It is true that such cases are rare, but after all we may well join with Dieulafoy in feeling surprised that they are not more frequent.

A detailed study of the treatment of enteritis would here be out of place. Doctors and patients are aware that it is almost entirely a matter of diet ; for enteritis with diarrhœa and intestinal putrefaction, the invariable rule is : no meat and as little nitrogenous food as possible. In the case of enteritis due to imperfect digestion in the stomach or small intestine, the poverty of the digestive juices is made up for by administering others such as gastrin and eukinase taken from healthy animals —a rational kind of opotherapy. In enteritis with constipation, treatment must be concentrated upon the latter, and will include massage, electricity, and mineral waters.

Accurate discrimination is a necessity in any system of treatment, for there can be nothing worse than to employ a remedy at the wrong time. It is not so very long since Mathieu and J. C. Roux pointed out the dangers of a too free use of enemata for the purpose of cleansing the intestinal mucous membrane. If we bring this section of our subject to a speedy conclusion, it is not because it is devoid of importance. Our object however, is to study the proper regimen for the cure and prevention of enteritis ; it is possible to formulate a code of dietetics which will be beneficial to every healthy individual.

As has already been stated, the large intestine, which is the seat of enteritis, contains food-materials already more or less transformed by the digestive juices, and legions of microbes. The latter are of two kinds : ærobic, those which cannot exist or thrive without oxygen, and anærobic, or those which develop only when not exposed to the action of oxygen. Among pathogenic microbes, the most active and most toxic are the anærobic,

such as, for example, the bacillus of tetanus and Pasteur's septic vibrio ; it is to microbes of this class that the serious character of appendix abscesses is due.

Our food, whether of animal or vegetable origin, contains several nutritive principles in varying proportions : proteids, such as the albumen of meat ; and carbohydrates, such as the sugars and starch, and fats. Food-stuffs of animal origin are generally richer in proteids than in carbohydrates ; those of vegetable origin on the other hand, are usually richer in carbohydrates than in proteids. Beef contains about 20 per cent. of albuminoids, and 0·60 per cent. of carbohydrates ; for cow's milk the corresponding figures are 4 per cent. and 5 per cent., and for eggs 12 per cent. and 0·5 per cent. The seeds of leguminous plants, such as haricot beans for instance, are relatively rich in proteids (24 per cent. as compared with 53 per cent. of carbohydrates). The flour of cereals, from which dough is made, is very rich in carbohydrates, and extremely poor in proteids (74 per cent. as against 9 per cent. in the case of wheat-flour). Proteids and carbohydrates come into play in intestinal fermentations, and in the antagonisms between species of microbes ; the treatment of enteritis is a problem both of microbiology and of diet.

If food-stuffs be impregnated with microbes and subjected to favourable conditions as regards heat and moisture, the microbes act like ferments, that is to say they decompose the nutritive materials and form new compounds. All microbes do not behave in the same manner ; some decompose carbohydrates, and, since the latter include the sugars, such microbes are termed "saccharolytes" ; others, known as "proteolytes," decompose nitrogenous matter. A microbe that performs only one of these functions is called a simple ferment, mixed ferments being those capable of decomposing both nitrogenous and saccharine matter. The microbes that inhabit the intestine consist of simple ferments which are exclusively proteolytes, and mixed ferments which are saccharolytes as well as proteolytes.

Saccharolytic microbes, which decompose farinaceous foods and sugars, produce chiefly acids, such as lactic, acetic, carbonic, succinic acid, &c. Proteolytic microbes, on the other hand, which decompose meat, form substances the majority

of which irritate the intestinal mucous membrane and are toxic to the organism : such substances include, among others, indol, scatol, cresol, and ammoniacal salts. By putrefaction of meat is understood complete fermentation, carried to an extreme, that is continuing until the formation of the bodies just enumerated. A microbe which converts sugars into acids cannot do so indefinitely, since the acids produced by it in the end impede its action, so that, when the culture medium has attained a certain degree of acidity, fermentation ceases. Each acid-producing ferment has its limit : the enterococcus is arrested by an acidity of 2·45 per 1,000 ; *Bacillus perfringens* (a pathogenic, anærobic microbe found in the intestine) by 1·60 per 1,000 ; *B. acidi paralactici*, one of the microbes forming lactic acid from milk, by 5·39 ; *B. bifidus*, of Tissier, an anærobic microbe of the intestinal flora of infants, by 4·90. It will be seen that the two microbes last mentioned withstand a considerable degree of acidity without their development being suspended.

Suppose that we place in a flask albuminoid matter (*e.g.*, meat), and sugar-containing matter (*e.g.*, milk), and then add to the contents of the flask two kinds of ferments ; a simple ferment, which decomposes only albuminoids ; and a mixed ferment, capable of decomposing both carbohydrates and albuminoids. The mixed ferment will convert the carbohydrate (*i.e.*, the sugar of milk) into acid. What will happen when the culture medium has attained a certain degree of acidity ? Since acid has an injurious effect upon bacteria, the development of the simple ferment will be arrested, and the decomposition of the nitrogenous matter will be suspended ; the mixed ferment, in its turn, will cease to take effect when it has produced to its own detriment the amount of acidity necessary to check its activity ; all further fermentation will then be prevented.

If, instead of a simple and a mixed ferment, we introduce into our flask two mixed ferments, arrested by degrees of acidity which we may represent respectively by the figures 3 and 4, it is evident that the development of the former will be checked sooner than that of the latter. Thus, the acidity of the medium having a restraining effect upon bacteria in general, a mixed ferment, capable of decomposing sugars and albumin,

is antagonistic to a simple ferment which decomposes albumin alone; and, if two mixed ferments be present, that which tolerates the higher degree of acidity will be antagonistic to one paralyzed by a smaller amount. Hence we have the following law enunciated by Tissier who, in conjunction with Bienstock, brought these facts to light:—In media containing albuminoid matters and more than 10 per 1,000 of sugar, a mixed ferment can arrest the action and development of a simple ferment; and a strong mixed ferment has the same effect upon a weak mixed ferment. These preventive influences are solely due to the quantity of acid produced by the bacteria in the course of their attack upon the carbohydrates.[1]

The course of events in the intestine is similar to that in the flask; the intestine contains both simple and mixed ferments, and also fermentable matters, both albumins and sugars; the putrefaction or extreme fermentation of the albuminoids will be arrested by the acids produced at the expense of the sugars. These concepts of general micro-biology furnish the key to the regimens recently proposed for the cure of enteritis.

It is now several years since Tissier, in studying the intestinal flora of infants, found that there are no microbes in the intestine of the newly-born child. After a few hours, however, an extremely rich microbic flora makes its way into the intestine through one or other extremity of the alimentary tract. A little latter a difference as regards intestinal microbes is observable between the breast-fed and the artificially fed infant; in the case of the breast-fed infant, about the third day the intestinal flora, which is by this time very rich, undergoes a reduction resulting in the survival of a small number of species of microbes, including one which predominates to such an extent that it is contained in the intestine as a nearly pure culture. This bacillus was first described by Tissier, who, on account of a peculiarity in its shape, gave it the name of *B. bifidus*. In the case of a child artificially fed with cow's milk, a reduction in the flora either does not occur or else takes place slowly and imperfectly, and it is found that such a

1 Tissier and Martelly, "Recherches sur la putréfaction de la viande de boucherie"; Tissier and Gasching, "Recherches sur la fermentation du lait," *Annales de l'Institut Pasteur*, December, 1902 and August, 1903.

child frequently suffers from the well-known intestinal disorder called infantile enteritis.[1]

The explanation is as follows: The milk received by the breast-fed infant is at once azotized and sweet (mother's milk being rich in sugar), and is decomposed by the ferments, simple and mixed, in the intestine. The mixed ferments include the *Bacillus bifidus*, which is a powerful ferment capable of producing and withstanding a considerable quantity of acid (4·90 per 1,000). This bacillus arrests the action of the remainder, consisting of weak mixed ferments and simple ferments. It is an anærobic microbe, which by itself possesses no pathogenic power, but, in decomposing the azotized matter, has the advantage of not giving rise to irritant or toxic products. *B. bifidus* checks intestinal putrefaction and preserves the health of the child. The artificially-fed infant, on the contrary, receives milk poorer in sugar and richer in azotized constituents; the less sugar the less acid, and the less acid the more abundant is the production of microbes. *B. bifidus* does not thrive, but indol and phenol are generated, and these are injurious to the mucous membrane and the whole system. Instead of nearly pure cultures of the beneficial *B. bifidus*, the motions of infants attacked by enteritis contain *B. perfringens*, an anærobic pathogenic organism, which is an active agent of putrefaction.

No doubt in order to produce such an attack of enteritis, there must also be predisposing causes, which are not rare and do not escape the observation of an acute practitioner. These include cracked nipples, an attack of lymphangitis which renders suckling painful, alteration in the milk due to the influence of food or weather changes—and even contagion, as shown by the following case recorded by Tissier, which has the value of an experiment:—

"Mrs. R. was nursing her daughter, aged 4 months; the latter had been under my own observation since birth, and had been uniformly healthy; her motions were absolutely normal, and contained no *B. perfringens.* Mrs. R. was requested by a lady of her acquaintance to suckle twice a day an infant

[1] H. Tissier, "Recherches sur la flore intestinale normale et pathologique du nourrisson" (1900). "Etude d'une variété d'infection intestinale chez le nourrisson": *Annales de l'Institut Pasteur*, May, 1905.

suffering from enteritis, with *B. perfringens* in its intestine. She did so, while continuing to nurse her own daughter. A week later the latter was seized with the same digestive trouble—diarrhœa of the same type and with the same microbes as in the case of the sick child ; contamination had taken place through the nipple. This case proves the infectious character of this form of enteritis. . . ."

In order to discover a remedy it was only necessary to trace the chain of phenomena back to its starting-point ; as the result of such a method of investigation, there was formulated a rational system of diet which, while applicable to the infant, is also beneficial to the adult who, being attacked by enteritis with intestinal putrefaction and diarrhœa, is threatened with the chronic form of the malady. The amount of azotized matter in the intestine must be reduced ; therefore let the infant be again breast-fed, and forbid meat in the case of the adult. Since carbohydrates must be increased, order the infant sweetened drinks, and put the adult on a vegetarian or lacto-vegetarian diet. In addition, take steps to cultivate the strong mixed ferments which, by their production of acid, are capable of arresting putrefaction.

As a matter of fact there is no reason why these beneficial microbes should not themselves be administered, and Tissier has therefore been led to prescribe cultures of *B. bifidus* and *B. acidi-paralactici*, the latter of which is a lactic ferment producing a large quantity of acid. Although not a panacea nor even an infallible remedy in all cases of enteritis, the treatment is a judicious one for enteritis due to intestinal putrefaction, and its value will be shown by experience.

The views of Dr. Combes[1] of Lausanne, with regard to the origin and treatment of enteritis, are not essentially different from the foregoing. His system, however, is intended to apply not only to infectious and diarrhœic enteritis, but also to the chronic muco-membranous type. The method is the same ; change the culture medium of the intestinal microbes ; replace putrescible, that is to say, azotized foods by saccharine ones, which act as antiseptics ; do not forget that milk and

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[1] "Traitement de l'entérite muco-membraneuse. L'auto-intoxication intestinale" (1906).

eggs are rich in nitrogen, therefore forbid them in acute enteritis or in exacerbations of the chronic form of the disease, and only allow them when the alimentary canal has already undergone repair. Antiseptic sugars are needed for foods which yield sugar in the upper regions of the digestive tract and, being more slowly decomposed than a sugar in solution, still yield it after reaching the large intestine.

The above is the essential prescription in the regimen. The flour of cereals and farinaceous foods surpass all other hydro-carbonated foods as regards their antiseptic qualities. In order to prevent putrefaction, they should be given as freely as possible at each meal at which albumen is taken, and farinaceous meals should be increased in number in order that the intestine may be constantly filled with this form of food. As for secondary prescripts, these are simply the current rules of hygiene for dyspeptics : not to drink while eating, or eat while drinking ; food to be taken in small quantities and frequently ; liquid and solid meals always to follow one another alternately ; lie down flat on the back or right side for an hour after each solid meal, but without going to sleep, &c.

The reception accorded to such a code of rules of health by the tired, anxious, and somewhat neurasthenic victim of enteritis will readily be understood, and for intestines worn out by epicureanism it is easy to realize the excellence of menus calculated to bring joy to Ceres and the nymphs of the springs at Evian. Dr. Combes has scored a well-merited success, due to sound physiological ideas, straightforward common-sense, and an extensive clinical experience. Were I, however, a French doctor, in order to treat the enteritis of Parisian ladies I would go and set up in practice at Lausanne. This is not meant ironically, since every physician is aware that treatment gains in efficacy if begun abroad. When a patient is in pain, is anxious about himself, and is losing his nerve, it is surely something to give him a change of air and surroundings, to remove him from the worry of business and social duties, and make him rest by sending him to another country. Once he is far away from places which remind him of his fatigue and anxieties, it is of the first importance to induce him to entrust himself to a doctor who will look after his diet, and, in the words of Rabelais, does not disdain to "contemplate, examine, consider, and philoso-

phize over the divinity that he find in his fæces. . ." It is well known that Switzerland is the country of good hotels, which willingly adapt their menus to medical prescriptions and serve up special diets, a feature which unfortunately is as yet all too rare in France.

Nevertheless enteritis can be cured in Paris, where the value of cereal foods and the resources of psychotherapy have been recognized for some time, and the beneficial results to be obtained from the establishment in the intestine of health-giving ferments are fully realized. Our medical men are conversant with modern science, which gravely comments on the refrain of the Pantagruelian chapter in which Rabelais narrates the requirements of Messer Gaster: "All for the bowels!" *(Tout pour la trippe!)*

The regimen of methodical frugality which cures enteritis should also be capable of acting as a prophylactic: from this therapeutic basis it is possible to derive the rules of a system of daily hygiene. In the intestine of every healthy subject there occurs fermentation, from which putrefaction normally arises: it is promoted by an excess of meat, and restrained by a hydrocarbonated diet. Why wait until an attack of enteritis renders the observance of these precepts imperatively necessary? The intestinal microbes must receive their due share of attention. The study is a complicated and laborious one, which captivated the attention of scientists long before it aroused the curiosity of the public outside the laboratories. It has been enthusiastically promoted by Metchnikoff, who approached the question by the precise methods of micro-biology, and has extended its horizons until he has given us a glimpse of a general system for the preservation of health and the amelioration of the conditions of existence. Exact studies and utilitarian tendencies are the foundation of experimental science, and we are too greatly interested in the success of these attempts to have any right to be ignorant of them.

Under natural conditions, the process of fermentation is of universal occurrence, leading to the display of the forces that, by decomposing and recomposing the bodies of animal and vegetable organisms, ensure the constant renewal of living matter. Fermentation is life, since it restores to life that which is dead.

These discoveries are pervaded by the work of Pasteur : fermentation is due to micro-organisms or living cells, and diseases are varieties of fermentation. The malting of barley for use in brewing, the making of wine and vinegar, the curdling of milk, and the manufacture of cheese are all instances of fermentation. Pasteur taught us how to discipline the forces that mankind had utilized for ages without understanding them ; empiricism has given place to rational methods, and resources are husbanded. As is well known, before curing animal and human diseases, Pasteur discovered the means of preventing the deterioration of wine and beer.

Fermentation also takes place in our own bodies, and the forms of it which constitute the most serious menace to health were the first to attract the attention of scientists. Infectious diseases are cases of fermentation, and the majority of toxins are ferments. It is with regard to digestive fermentation, both gastric and intestinal, that our knowledge is most deficient. "Numerous attempts," writes Metchnikoff, "are made to regularize various kinds of fermentation by the aid of pure cultures, and to improve the making of wine, cider, and cheese ; it is high time that analogous methods were employed in order to perfect intestinal fermentations in man. Our intestinal flora should be considered as a wild flora, which has developed without the conscious assistance of man ; the endeavour must be made to transform this wild flora into a cultivated one, represented by benign or at least harmless species." The first requisite is to know the normal and pathological flora of the intestine.

The quantity of microbes contained in and discharged from the intestine is so enormous that it is difficult to form an estimate of it, even by means of approximate figures ; it will therefore be sufficient if we get some idea of the gigantic totals given by various authors. According to Vignal[1] and Suckdorf,[2] man voids from thirty to fifty milliards of microbes per day, while A. Klein, of Amsterdam, places the total at 8,800 milliards, 99 per cent. of which he considers are already dead when

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[1] *Comptes Rendus Hebdomadaires des Séances de l'Academie des Sciences*, t.cv, 1887.

[2] *Archiv für Hygiene*, Bd. iv., 1886.

expelled. Strasburger gives the fantastic figure of 128,000 milliards, but the discrepancy between these numbers is of much less importance than it appears. The scientists by whom these calculations have been attempted have not employed the same methods ; if all the microbes seen in a dilution be counted, without distinguishing whether they are dead or alive, many more are found than if cultures be made and the resultant colonies counted. The reason is that the dead microbes do not give rise to colonies, though before perishing they have played their part in the intestine. If ærobic culture media be used, no colonies result from the anærobic microbes, and *vice versâ*, although there are legions of anærobic intestinal microbes. Figures which are approximately correct are not worth the trouble that they may cost to obtain. Just as in the case of microbes in water, so in that of those in the intestine, it is of much less importance to determine the actual number than to know which are pathogenic. A litre of water containing only a hundred microbes is dangerous if these micro-organisms happen to be those of typhus or cholera.

As regards a qualitative analysis, from 27 to 45 intestinal species have been described by different investigators.

These microbes are not uniformly distributed throughout the entire length of the digestive tract, since there are far fewer in the small intestine than in the cæcum and colon. It has even been proved that the digestive juices of the small intestine have a bactericidal action, and destroy microbes. In the case of an infant, according to the investigations of Tissier, carried out under the direction of Metchnikoff, microbes are rare in the stomach, very rare in the duodenum and the first portion of the small intestine, and present in increasing abundance in the ileum, cæcum, and rectum. In the upper regions of the digestive canal, to which air and oxygen have access, are found the ærobic species ; the anærobic forms occur in the large intestine, since the oxygen has been exhausted before this is reached.

The truth of the foregoing generalizations has been confirmed by investigations upon animals, which have also shown that the flora varies with the diet. Lembke modified the intestinal flora of dogs by giving them animal and vegetable food alternately, or by administering to them cultures of

microbes prepared in the laboratory stove. Such methods long ago led to the important conclusion that the intestinal flora is capable of modification, and that we possess several means of modifying it.

We are at once confronted with the question whether these microbes are useful or the reverse, and Pasteur sought to discover whether they are indispensable to normal digestion. If they be indispensable, we should expect to find them abounding to the same extent in all animals, but this is not the case. In parrots, both young and old, the intestinal flora is very poor, and Cohendy, working in conjunction with Metchnikoff, only succeeded in discovering five species of microbes in these birds. In the alligator, Cohendy found a flora several hundred times poorer than that of man.

Other scientists, with a view to deciding the question of the utility of the microbes by means of experiments, endeavoured to rear young animals aseptically, by shielding them from all germs. Nothing could require more delicate management or greater exactness of treatment than these experiments, and there is nothing that demands a longer period of patience. They have not often been repeated, and in fact have not been repeated often enough ; they have a classic value and are worth remembering. Nuttall and Thierfelder extracted fœtal guinea-pigs from the abdomen of the mother, by cæsarean section, and fed them in sterile receptacles, with sterilized milk and biscuits.[1] The little guinea-pigs throve fairly well, though their growth was somewhat slower than that of guinea-pig controls, kept under natural conditions. Schottelius performed the same experiment with young chicks, which, however, did not take kindly to aseptic life, and sank into a feeble condition, which lasted until microbes were added to their food.[2] Madame Metchnikoff succeeded in rearing aseptically a batch of tadpoles, which developed tolerably well and even outlived a brood of controls, although the process of rearing them was slower and more difficult than development under normal conditions, and, in spite of their relative longevity, the artificially-reared tadpoles were stunted.[3] I am bound to

[1] *Zeitschrift für physiologische Chemie*, Bd. xxi., 1895.

[2] *Archiv. für Hygiene*, Bd. xxxiv., 1899.

[3] *Annales de l'Institut Pasteur*, t. xv., 1901.

admit that no one has yet attempted to rear a human infant aseptically.

Thus, according to the experiment of Nuttall and Thierfelder, the microbes are useless, while the results obtained by Schottelius and Madame Metchnikoff would seem to show that they are indispensable, or at least useful. There is, however, no contradiction here, since the experiments were not made under the same conditions ; guinea-pigs are not chicks and the needs of birds may not be the same as those of mammals. We are still ignorant as to the food that is best suited to a particular species ; on another regimen the young guinea-pigs of Nuttall and Thierfelder might perhaps have died, whilst Schottelius's chicks might have thriven. These experiments would have to be repeated a number of times before we should have the right to draw a conclusion from them, but other facts tend to prove that the microbes are not indispensable to digestion ; they are very rare in the small intestine, which is precisely the region in which useful digestion takes place ; moreover, in the case of certain animals, such as scorpions and the larvæ of several species of mites (belonging to the genera *Galleria*, *Tinea*, &c.), digestion is efficiently performed in a sterile intestine. From his investigations upon human infants, Tissier concludes that the microbic fermentations in the intestine of the infant are of very little importance, and that none of the bodies resulting therefrom is necessary to the organism *for its digestion*.

If the intestinal microbes serve no useful purpose they may certainly be injurious, as is shown by the existence of enteritis. Peritonitis as the result of perforation is another proof of this ; when a man who has received a sword-thrust in the abdomen succumbs to an attack of acute peritonitis, the reason is that the microbes from the intestine have escaped into the peritoneal cavity—a danger that would not exist were the intestine aseptic. For the microbes to pass from the intestine into other parts of the body, it is not even necessary that the intestine be perforated. Von Behring's investigations into the origin of tuberculosis, and other work that has been done on the same subject, have shown that the tubercle bacillus can penetrate into the lung by way of the alimentary canal ; after being swallowed, it passes through the mucous membrane of the intestine, which

it leaves *intact*, and reaches the lymphatic glands of the mesentery and thorax. Calmette has recently advanced the hypothesis that this permeability of the intestinal wall explains a number of cases of pulmonary infection in infants, due to microbes which very frequently occur in the mouths of healthy subjects. These micro-organisms reach the lung by way of the abdomen, after being swallowed, and, if disease eventually results, the reason is that a chill, or other predisposing factor, has caused a hitherto harmless germ to become virulent.

It is not sufficient to concern ourselves with acute disease alone ; the intestinal microbes are capable of doing a great deal of harm without attracting much attention, provided that they be given sufficient time. They carry the decomposition of azotized matter to an extreme, setting at liberty the bodies that have already been mentioned, such as indol, scatol, and ammoniacal compounds, which irritate the mucous membrane, spread through the system, and are capable of affecting the walls of the vessels in which they circulate, and the nerves with which they come into contact.

Everyone is acquainted with the work of Bouchard upon auto-intoxication, which was carried out before the era of microbiological investigations upon digestion. There are too many anærobic microbes in the intestine, and we know too well that a number of those that have been found there are eminently capable of producing toxins and poisons, not to be sure that the microbes count for a great deal in the cases of auto-intoxication mentioned by Bouchard. There is no exaggeration in accusing them at least of complicity in nervous fatigue, hardening of the arteries (arterio-sclerosis), many an affection of the skin, and the diseases still imperfectly understood which result from gout. As an antidote to this chronic poisoning in minimal doses, common sense would suggest the employment of the regimen that contributes to the cure of intestinal putrefaction. This is the principle of that alimentary hygiene which is preached by Metchnikoff with so much enthusiasm, verve, and humour, and with such an abundance of facts and arguments.

The large intestine is the region of intestinal putrefaction ; the following paragraph in which it is attacked will be within the memory of anyone who has read " Etudes sur la Nature Humaine " :—

"The development of the large intestine in mammals is due to the fact that it formed a receptacle for waste food-materials, and consequently enabled these animals to run for a long time without stopping, which was an advantage in the struggle for existence. On the other hand, the microbes that multiply so abundantly in the contents of the large intestine facilitated the utilization of certain indigestible substances, such as cellulose. These circumstances, however, have lost their value in the case of the human species. . . . Man no longer captures his prey by means of a rapid chase, and the culinary art and the culture of plants suitable for food provide him with resources beyond the reach of the lower animals. Mammals, moreover, are outlived by birds, and have acquired the advantage of a large intestine at the expense of longevity. Now, in birds, which have no large intestine, the microbe flora is incomparably poorer than that of mammals. Ostriches are the only birds in which the large intestine is highly developed, and they, according to the estimate of M. Rivière, who is engaged in Algeria in breeding them, instead of living longer than much smaller birds, such as parrots, crows, swans, &c, do not attain the age of 35 years. . . ."

The example afforded by birds, in which the large intestine is of small dimensions, must be supplemented by that of human beings, who have lost the use of this section of the alimentary canal. Surgical records mention the case of a woman who, as the result of an operation, was deprived of the use of her large intestine for six months; her digestion was good, and she increased in weight. In 1894 two Russian surgeons reported the case of an old woman, whose motions for thirty-seven years had been passed through an intestinal fistula; this infirmity had not prevented her "from marrying, having three children, and earning her living by hard work." Thirty-five years after the formation of the fistula, an abdominal operation revealed the fact that the large intestine had atrophied altogether. When its function ceases an organ disappears.

Must we, then, have our large intestine removed? "In spite of the great progress achieved by surgery, the excision of the large intestine cannot be dreamt of in our time; in the distant future perhaps it may be undertaken." What would Ambroise Paré have thought, had it been predicted that towards

the end of the nineteenth century surgeons would readily perform operations such as :—causing the intestine to open into the stomach by an incision, removal of the gall-bladder, excision of a kidney, or stitching up a heart? It may be added that the excision of the large intestine has already been performed by an English surgeon, Dr. Arbuthnot Lane.

The practical method consists in eliminating the large intestine by hygiene, in, so far as possible, putting an end to intestinal putrefaction, and in producing in the intestine the conditions by which the putrefaction of meat or of milk is suspended in a flask containing microbes. The preventive action of microbes such as *Bacillus acidi paralactici* is due to the production of a considerable quantity of lactic acid, which is formed at the expense of lactose or sugar of milk. The simplest plan would therefore be to take at each meal a definite quantity of lactic acid already prepared ; it has however been shown by experiment that much better results are obtained if ferments which produce lactic acid be swallowed in the form of microbes. The latter reach the intestine alive, and, in order that they may produce lactic acid must be furnished with sugar ; it is for this reason that the diet should contain a substantial proportion of carbohydrates. Sugar and water would not do, since it is absorbed long before reaching the large intestine. The sugar must be provided by solid food-stuffs, which, on entering the large intestine, are not yet completely digested, so that they carry the supply of sugar as far as possible. Sweet fruits, preserves, and sweet vegetables, such as beet-root, answer the purpose very well. As for the salutary microbes, they are swallowed either in cultures, or in the natural form of sour milk.

The practice of preserving meat in sour whey, which prevents it from putrefying, has been in vogue in certain countries for a considerable period ; it is lactic acid that keeps vegetables stored in pits from rotting, and it is lactic acid that from time immemorial has served to preserve milk in the form of cheese. There is lactic acid in rye-bread, as also in the *kvass* of the Russian peasants. To it are due the excellent properties of the *kephir* of the Caucasians, the *koumiss* of the Tartars, the *lebenraib* of the Egyptians, the *yaourth* or *yoghourt* of the Balkan peoples, and the *prostokvacha* and *varenetz* of the Russians. Curdled milk is the national food of the Mpeseni of

South Africa ; the Asseoue, near Lake Tanganyika, the Zulus and the Wankande consume milk only in the form of fresh cheese, mixing with it salt and pimento. Metchnikoff states, on the authority of Dr. Lima, of Mossamedes, that a number of native tribes in Southern Angolo live almost exclusively on milk. "They use the cream for rubbing into the skin, in order to render it more supple, while the sour and curdled milk serves them for food." Health is good in all these tribes ; numerous instances of longevity are met with, as also "many old people who are very active and capable of making long journeys."

For a period of six months Dr. Cohendy made an experiment upon himself, which consisted in adopting in succession : a mixed regimen, composed of vegetables, flour, and meat ; an exclusively carneous diet; and a regimen without meat, but with the addition of a beneficial microbe, in the shape of a lactic ferment.[1] Chemical analyses showed that the sulpho-conjugate ethers excreted, which are indices of intestinal putrefaction, were much more abundant with the carneous than with the mixed regimen, and sank to a minimum with the lactic-vegetarian diet. In accordance with Metchnikoff's idea, the same experimenter endeavoured to get lactic ferments to become domiciled in his intestine, and came to the conclusion that a species of microbe foreign to the usual denizens of the intestine may become acclimatized there, without a special regimen being necessary. There is no need to cut off meat, except in a case of enteritis. It is recommended that a lactic cure be taken periodically, like an air cure or course of medicinal waters ; sweet foods are useful adjuvants.

Professor Metchnikoff has been good enough to inform us of the results of some as yet unpublished investigations, which have been carried out in his laboratory by Dr. Belonowsky, who has made a close study of the antiseptic action of lactic ferments in mice, and especially of ferments administered alive. If milk, after being curdled with the selected microbe, be heated to 100° C. (212° F.), intestinal disinfection no longer takes place ; but if it be heated only to 56° C. (132·8° F.), disinfection occurs, although less thoroughly than with the living microbe. Microbiologists have long been acquainted with this method of heating

[1] *Comptes Rendus de la Société de Biologie*, March 1906.

to different temperatures, by means of which it is possible to distinguish bodies, and especially ferments, owing to the difference in their powers of resistance. Thus we find that among the products of the lactic ferment there is a substance destroyed at 56° C. (132·8° F.), which assists in disinfecting the intestine owing to the antagonism displayed by it towards other intestinal microbes. It would appear that this property, which is possessed by the lactic ferments in an eminent degree, is not peculiar to them ; recent investigations show that a culture of any microbe produces bodies which are noxious, both to itself and to other species of microbes, and that the energy of these substances exceeds even the antiseptic power of phenic acid. This discovery reveals a novel phase of the struggle for existence.

The choice of the microbe that is to reinvigorate mind and body must not be left to chance ; it is well to select a pure ferment, not associated with other microbes, the causative agents of other fermentations, or with yeasts which produce alcohol. It is possible that, besides the lactic fermentation sought for, a given microbe may cause another fermentation less salutary or less agreeable. The so-called "Bulgarian bacillus," which has been isolated from various kinds of curdled milk, and does not exist only in Bulgaria, possesses the advantage of producing a large quantity of lactic acid, and the inconvenience of imparting to the milk an unpleasant taste due to the fermentation of the fats. Several good ferments, chosen by experiment, can be associated together, just as several vegetables may be associated in the same dish. It is recommended that the sour milk be prepared from milk which has been skimmed and boiled : skimmed, in order to avoid the fermentation of the fat and the disagreeable taste resulting therefrom ; boiled, in order to kill the bacilli that it may contain at the outset ; this is a hygienic precaution of general application. "As regards the problem with which we are dealing," says Metchnikoff, "practical measures would therefore consist either in drinking sour milk, prepared with a combination of lactic bacteria, or in swallowing pure cultures of the Bulgarian bacillus (which thrives very well under the conditions afforded by the intestine), together with a certain quantity of sugar of milk, or of saccharose (ordinary refined sugar)."

The author of "Étude sur la vieillesse" does not proclaim these microbes as *the cure for old age.* "It is for a more or less distant future to form an opinion on this question." This opinion, however, can already be divined. From a frugal regimen, which prevents intestinal putrefaction, and prescribes abstention from uncooked fruit and vegetables—carriers of unknown microbes and frequently watered with human excreta—it is permissible to expect some amelioration in general health, which is equivalent to a prolongation of youth. Discretion in diet therefore forms an essential part of the system. With Metchnikoff, we cannot fail to be interested in old folk who retain their vigour and intelligence to the last, and, even though we be not jealous of all centenarians, we would at least escape premature decay.

"Among the centenarians mentioned in M. Chemin's paper, there are several who made milk-food their staple diet. Thus, in Haute-Garonne, Mlle. Marie Priou, who died in 1838, aged 158, with all her faculties unimpaired, for the last ten years of her life subsisted only on cheese and goat's milk. Ambroise Jantet, a farm labourer of Verdun, who died in 1751, aged 111, ate only unleavened barley bread and drank nothing but water and whey. A woman, named Nicole Marc, a hunchback and a cripple, who died at the Château of Colemberg (Pas-de-Calais), aged 110, lived only on bread and milk-food; it was not until towards the end of her life that she was induced to take a little wine. We are indebted to the courtesy of M. Simine, an engineer in the Caucasus, for the following particulars, taken from the *Tiflissky Listok*, of October 8, 1904. In the village of Sba, in the Gori district, there lives an old Ossetian woman, named Thense Abalva, whose age is estimated at about 180. She is still in fairly good health, and is able to sew and to attend to her household duties; although bent, she walks with a fairly firm step. She rises early, has always been a total abstainer, and her food is chiefly composed of barley bread and butter-milk, which is extremely rich in lactic microbes" (Metchnikoff, "Étude sur la Nature Humaine.")

There are conclusions to be drawn from the foregoing facts. The story of the struggle against infectious disease has given rise to the almost invariable idea that microbes are harmful, though there are some which are good even from the human

point of view. There are microbes that work for us outside our bodies; these are the causative agents in all cases of fermentation, whether natural or artificially produced for industrial purposes. There are others which work within us, as, for instance, *Bacillus bifidus*, which purifies the intestine of the infant, or those lactic microbes that human instinct has always sought after, and that can be acclimatized to our advantage by means of a rational regimen. We weed our gardens and vineyards, and clear our trees from caterpillars; why not replace the noxious microbes in our bodies by others which are beneficial?

The treatment of enteritis, like that of dyspepsia, gout, diabetes, obesity, and the so-called maladies of nutrition in general, has at length led to the belief that medicine consists, not in temporary and more or less miraculous interventions, but in a system which opposes natural phenomena by other natural phenomena which we are able to provoke. For, chronic diseases, chronic remedies. Vaccination and serotherapy are typical scientific remedies, and regimens are scientific remedies of another kind, which have caused cookery to enter into medicine, so that the cookery-book has become the natural ally of the Pharmacopœia. The doctor, who is already skilled in psychiatry, now condescends to learn to be a "gastrolater."

Frugality and sobriety are becoming fashionable. They may perhaps be carried to excess, but it is pleasing to see science bringing mankind and medicine back to nature, according to the ideas of Rabelais, Molière, and Rousseau.

The subject of enteritis is a lesson in scientific optimism, in which the final motto is the same as in the romance of "Candide," "We must cultivate our garden."

VARIOLA AND VACCINIA.

THE WORK OF JENNER.

I.

Bygone authorities gave the most realistic descriptions of variola, for even the doctor most hardened by familiarity with the evils to which poor humanity is subject lost his self-possession when confronted with such an accumulation of miseries. A general but approximately correct idea of the characteristics of variola may be obtained by imagining the deadliness of some great infectious and contagious disease, and the pitiable prostration caused by severe fevers, with the addition of the disfigurements, swellings, suppuration, pustules, scabs and crusts seen in the most disgusting skin diseases.

A spot that increases in size becomes swollen and raised, then a vesicle full of fluid, and finally an abscess which discharges pus—such is the primary accident that repeats itself all over the body. The eruption exhibits varying degrees of severity, according as the pustules remain distinct (discrete variola), are grouped together into clusters (corymbose variola), are numerous and contiguous (like shagreen seen under an enormous magnifying glass), or coalesced into extensive blebs (confluent variola). It invades the conjunctiva, as also the mucous membrane of the nasal fossæ, mouth and large bronchi. The papules, which, in the words of Trousseau, at first resemble spots of pure wax, begin to suppurate about the seventh day, and when they commence to dry up their secretion looks like dirty honey. The eyelids are swollen, the eyes closed, and there is swelling of the ears and jaws; the nostrils are obstructed by yellowish crusts, the lips are furred and bleeding, and the skin gives off a fetid odour. The whole epidermis of the face is swollen to such an extent as to form a hideous parchment-like mask; the voice is raucous, and broken by fits of coughing and paroxysms of suffocation. In

hæmorrhagic variola—black variola—the blood blackens the pustules, or spreads beneath the skin in large bluish patches, producing a livid appearance similar to that sometimes seen in dead bodies, so that the patient might be supposed to have been plunged into a vat of grapes. The mind is perfectly clear. "The patients suffering from hæmorrhagic variola were not delirious for a moment. They conversed with us, and asked us to relieve them with an absolutely unclouded intelligence" (Legrand du Saulle).

Some idea of what was formerly the condition of those who recovered from small-pox may be gathered from the accounts of old authors, who had an extensive experience of the disease. The naïve description of Valentin and Dezoteux[1] is reminiscent, in its quaintness at least, of the state of Pangloss after the cure. "If the patients do not succumb to the deplorable and grievous condition to which they are reduced, they languish under misfortunes more cruel than death itself, or are doomed to be infirm or crippled for the remainder of their lives. Beauty, that precious gift of nature, and finely chiselled features disappear beneath the hideous traces left by this poison. While many are disfigured, others lose their sight or hearing; some have red eyelids, constant epiphora, ophthalmia, lippitude, the nasal duct indurated or obstructed, and the puncta lachrymalia altered or destroyed; in other cases the lips are swollen, the nostrils occluded, and the nose is eaten away or disfigured by scars. Many are afflicted with gatherings of considerable size and abscesses in different parts of the body, caries, denudation of the bones, and ulcers. A clothworker at Sedan had six children attacked at the same time; five of them became blind, and the sixth lost an eye. What desolation in one family!"

An epidemic of variola was formerly almost as deadly as an epidemic of plague. From 1661 to 1772, writes Odier, there died in London 2,538,450 persons, of whom 193,432, or at least one in fourteen, perished from small-pox; at Geneva in the same period the deaths were 76,050, of which 3,972, or

[1] "Traité historique et pratique de l'inoculation," by the citizens François Dezoteux and Louis Valentin, doctors of medicine. Paris, year VIII. of the Republic (1799-1800).

more than one in nineteen, were due to small-pox. Bernouilli believed that small-pox was responsible for the deaths of about 600,000 people every year, and Cullen states that at Glasgow in 1768 there was an epidemic so fatal that scarcely one patient in ten escaped. In many an epidemic in Paris the deaths were one in seven ; more than 2,000 children died at Montpellier in 1744, while in 1720 there were 20,000 victims in Paris alone. One year with another, the number of cases of variola in Paris was at least 12,000. One saw "whole families carried off, villages depopulated, manufactures arrested, commercial towns ruined, provinces desolated, and sometimes the course of justice suspended." Whence we have the saying of La Condamine : "None are exempt from small-pox but those who do not live long enough to await it."

Old documents have been searched by savants in order to discover the origin of variola. To the Greeks and Romans it was probably unknown ; whether it came from Ethiopia or Arabia, the earliest accounts of it were written by the Arabs, and its appearance in Europe followed the Arab invasions. From Europe the disease travelled to the New World, reaching Hayti in 1517, Mexico in 1518, Boston in 1649, and South Carolina in 1783. In France, the first mention worthy of credence would appear to be that in the chronicle of Marius, Bishop of Avranches, about 580. In 582 Gregory of Tours and his clerk Armentarius are said to have had small-pox ; they recovered through the intervention of St. Martin.

The notion of contagion is as old as the disease itself, which is contagious in the strict sense of the term ; that is to say, that contact with the patient or with objects and linen which have touched him is sufficient to communicate the infection, from the first day of the eruption as stated by some, or even from the prodromal period according to others. There is no doubt that contagion can also take place at a distance ; the germ floats and travels through the air, but contagion of this kind is diminished in rainy weather.[1]

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[1] From 1891 to 1895, when small-pox was prevalent in London, many cases were treated on hospital-ships in the Thames, whence the disease was transmitted to the riverside villages. Dr. Thresh, Medical Officer of Health for the County of Essex, observed that within a radius of three-quarters of a mile

Variola is contracted through the skin or the respiratory passages; the virus on being inhaled makes its way into the blood, spreads all through the system, and multiplies in the skin. There is usually a great difference between variola contracted through the skin and that resulting from inhalation, although the disease is invariably marked by a cutaneous eruption.

The microbe of variola is still unknown, but the prophylactics employed are the general methods taught by the school of Pasteur. In olden times the etiology of the disease was veiled in mystery, and the knowledge on the subject may be summed up fairly well in the distressingly inaccurate aphorism of Mackenzie, who stated that small-pox may suddenly supervene immediately after a bout of debauchery, intemperance, or sexual excess, after indispensable night work, compulsory toil, or necessary journeys. The germ was sought for in the decomposition of the watery fluid surrounding the fœtus, and it was proposed to extirpate it by squeezing out the umbilical cord immediately after birth, a practice recommended by the Chinese doctors. "There are still," writes Valentin, "families which base their security on this usage. Cases have even occurred in which practitioners have lost their children from small-pox, although they have squeezed out the cord and expelled the blood from the umbilical vein *with all paternal solicitude.*"

As for treatment, everything was brought into use—superstitions and pharmacopœia, fetiches and plasters, purges, bleedings, ointments, caustics and emollients, unopened heads of certain flowers, tisanes, baths, opium, mercury, quinquina, camphor, and antimony: were it not for vaccination, we should to-day be scarcely more advanced than the Hungarian Jews, who were said to protect their children by sprinkling them with salt as soon as they were born.

It was, however, observed that as a rule the same individual only has variola once. Van Swieten remarked that, in a

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8·8 per cent. of the total population were attacked; beyond this radius only 2·4 per cent., and in the district of the Orsett Union, still further distant, only 0·65 per cent. were attacked; in the Purfleet district, exposed to the prevailing winds, and in that to the north, towards which the wind hardly ever blew, the percentage of those attacked was 12 and 1 respectively.

practice extending over thirty years, he had not seen a single case of a second attack. That the disease does not recur is a fact of primary importance, which was the origin of inoculation and vaccination according to the methods of Jenner and Pasteur.

Before the introduction of vaccination by Jenner, *inoculation* or *variolisation* was practised, that is to say, *the actual virus of variola*, taken from a patient suffering from the disease, was inoculated at a certain spot in the skin. The result of this operation was an attack of artificial small-pox, which was very much milder than the natural disease. At each puncture a pustule developed, followed on the eighth day by a discrete eruption on the body; the patient almost always recovered, and remained immune.

Whence inoculation came and the name of its discoverer are alike unknown. In Asia and Africa it had been practised from time immemorial, by an empiricism more or less mixed with superstition, but it was not introduced into Western Europe until the eighteenth century. The note of enthusiasm with which it was received at this epoch of wisdom and virtue has been preserved in the work by Valentin and Dezoteux, to which allusion has already been made. The story, as told by these authors, and by Voltaire in his "Eleventh Philosophical Letter," is as follows:—

"In Georgia, Circassia, and Arabia the insertion of small-pox appears to have been invented by poor, rough, and illiterate people, by obscure women who at first practised it quietly and without attracting public attention. It was the product of base interest, of sordid avarice, and not of reasoned knowledge. The nations of the Orient at first made use of it in order to preserve the beauty of their daughters, and to protect it from the ravages that are the ordinary consequence of natural small-pox; ravages which, by impairing this beauty, very considerably diminished the revenue from the infamous trade carried on by these races for the purpose of supplying the seraglio or harem of the sovereigns of Asia" (Valentin and Dezoteux, *op. cit.*).

"The Circassians are poor and their daughters beautiful; consequently it is in them that their greatest traffic is carried on. They provide beauties for the harems of the Sultan, the

Shah of Persia, and those who are rich enough to buy and maintain such costly merchandise. . . . Now, it frequently happened that parents, after taking great pains to give their children a good education, found their hopes suddenly frustrated. Small-pox broke out in the family, and when one daughter died of it, another lost an eye, and the beauty of a third who recovered was destroyed by an enlarged nose ; the poor people were irretrievably ruined. Often, indeed, when small-pox became epidemic, the traffic was interrupted for many years, which caused a notable reduction in the seraglios of Turkey and Persia. . . .

"It was noticed by the Circassians that in six thousand people there was scarcely a single individual who was attacked twice by really acute small-pox ; that although the same person might sometimes certainly have three or four slight attacks, he never had two of a pronounced and dangerous type ; that, in short, no one ever really suffers from this disease twice in his life. They also observed that when small-pox occurs in a very mild form, and the eruption is unable to break through any but a fine and delicate skin, no mark is left on the face. From these natural observations they concluded that, if a child had a mild attack of small-pox at the age of six months or one year, it would not die of it, would not be marked, and would be quit of the disease for the rest of its days. In order, therefore, to preserve the lives and the beauty of their children, what had to be done was to give them small-pox at an early stage : this was effected by introducing into the body of the child the contents of a pustule taken from the severest and at the same time most favourable case of the disease that could be found. The experiment could not fail to succeed. The Turks, who are sensible people, soon afterwards adopted the practice and to-day every pasha in Constantinople gives small-pox to his son or daughter when old enough to be weaned" (From the "Eleventh Letter" of Voltaire, written in 1727).

From Asia the system of inoculation passed into Greece ; it was at Constantinople that it first came under the observation of Western physicians.

During the great epidemic of 1701 those who had previously been inoculated with small-pox escaped or recovered. The fact attracted the attention of Dr. Timoni, physician to the

Sultan, and Dr. Pilarini, physician to the Czar of Russia, who was staying at Constantinople at the time, and they introduced inoculation to the Greeks, Armenians, and inhabitants of Western Europe. "In this way inoculation passed from the cottages of the people into the houses of the rich and the dwellings of persons of distinction, and commenced to assume a favourable aspect."

Timoni did not fail to visit two *female doctors*, the Turkish celebrities of the period in the matter of inoculation. One of these women, known as "the old Thessalian," in order to procure the variolar virus, punctured with a triangular needle several pustules on the legs and backs of the thighs of some child of healthy constitution, who was suffering from natural small-pox, of the "discrete" kind. The person to be inoculated, who for five days had been obliged to abstain from meat, eggs, wine and other heating liquors, and had been duly purged the day before, was pricked in the parts of the body corresponding to those from which the virus had been taken. A poultice of acorn husks and angelica leaves was applied to the punctures for a few hours, and then all that remained to be done was to live, for at least thirty days, on vegetables and soups made from barley or flour. The first symptoms of artificial variola appeared on the seventh day. The other woman, who was less simple or more shrewd, said that inoculation had been revealed to her by the Holy Virgin; in order to sanctify the operation, she accompanied it with signs of the cross and prayers, and her pay had to be supplemented by gifts of candles for the altar of the Virgin. She made the punctures on the forehead, near each ear, and on the chin, so as to form a Greek cross; the clergy, to whom she offered a plentiful supply of candles, sent her patients, and she boasted of having performed more than 40,000 inoculations. The system of inoculating by punctures is that which prevailed a little later in Western Europe.

In China, small-pox was "communicated" in another manner. Crusts from pustules were preserved in a small, well-stoppered, porcelain vessel; for use, they were pulverised and placed in a tiny cotton bag with a grain of musk, so as to form a pastille, which was then introduced into the nostril and left there until the first symptoms appeared. In former times the nostrils were painted with a brush dipped in fresh virus. In Hindustan the Brahmins performed inoculations by means of small incisions;

in the Nile Delta the operation was known as "the purchase of small-pox." Women fastened a cotton band round the arm of a small-pox patient, in such a way that it became impregnated with virus; on returning from market, they took off the band and applied it to the arm of the child to be inoculated.

In 1713 Dr. Timoni, "of the Faculties of Padua and Oxford," related what he had witnessed at Constantinople, and in 1715 Pilarini caused to be printed at Venice a pamphlet which circulated through Europe. In 1716 Antoine Leduc, a young bachelor of the University of Leyden, who was born at Constantinople and had himself been inoculated as a child, defended for his doctor's degree a thesis on the insertion of small-pox. The Marquis de Chateauneuf, French Ambassador to the Sublime Porte, had his three children inoculated, but it was a woman who won over Western Europe to the principle of inoculation.

Lady Mary Wortley Montague, wife of the English Ambassador at Constantinople, had her son, aged six, inoculated by her surgeon (Maitland) in 1717; on returning to England in 1721 she had her daughter inoculated in the presence of the Court physicians. Shortly afterwards the Princess of Wales, having nearly lost a daughter from small-pox, desired to have all her family inoculated and asked the sanction of the King, who required that the experiment should first be repeated on others. The operation having been performed upon seven condemned criminals, and afterwards upon five children of the parish of St. James, the whole royal family was inoculated.

In 1738, when a severe epidemic broke out in Middlesex, 2,000 persons had themselves inoculated and "all escaped." In 1746, under the auspices of the Government, a society under the presidency of the Duke of Marlborough founded a hospital for the inoculation of country-folk and poor townspeople. At that time inoculation was performed either by means of small incisions, by scraping the skin with a penknife, by means of blisters, or by inserting into the skin a piece of thread charged with virus. About the year 1767 the brothers Sutton acquired an immense reputation and an enormous fortune by inoculating by means of a simple puncture with the lancet.[1]

[1] "Daniel Sutton had established two inoculation-houses in Essex, where he commenced by inoculating the poor; but since these no longer sufficed for the

This success more than once narrowly escaped a check. In Paris it was rumoured that several people of distinction had died in London from the effects of inoculation, and that the practice had been abandoned in England: the Sorbonne, in spite of Helvétius and Astruc, had condemned it. In England even, inoculation was denounced from the pulpit as the invention of the Evil One. "This is as true," cried Massey, "as that the devil of old gave Job confluent small-pox; thus, it is the atheist and the profane, the pagan and the infidel, who inoculate and get themselves inoculated." "This preacher was cut out for a Capuchin," said Voltaire, "and scarcely deserved to have been born in England. Prejudice entered the pulpit first, and reason only followed after: this is how the human mind usually acts." As a matter of fact, inoculation was almost abandoned from 1720 to 1750; in 1752, however, in the church of the hospital founded by the Duke of Marlborough, a sermon in favour of inoculation was preached by the Bishop of Worcester, and five editions of it were printed in one year.

De la Coste, a French physician, having brought the first news from London in 1723, the Duke of Orleans desired that the experiments should be repeated, but his death put a stop to the movement. The "magical operation" was discredited by theses from the School of Medicine, and almost forgotten. "What!" said Voltaire, "do not the French want to live, or have their women no care for their beauty? Verily we are a strange people! In ten years' time, perhaps, this English system will be adopted, if the priests and the doctors permit; or else the French, in three months, will avail themselves of inoculation out of caprice, if the English become tired of it through inconstancy."

It was not until 1754, on the reopening of the Academy of Sciences, that La Condamine read his memoir on the inocula-

accommodation of those who flocked thither, barns, stables, and sheds were soon filled with the inoculated. There were children under two months, and old people over seventy years of age. Harvesters did not lose a single day's work, and all recovered: but people became jealous of Sutton, and a charge was made against him at Chelmsford assizes. On his appearance, accompanied by a large number of persons whom he had inoculated, he was received with applause, and the jury, instead of finding him guilty, declared that he deserved encouragement and public recognition."—(Valentin and Dezoteux.)

tion of small-pox, which was immediately printed, translated into English, Italian, and Spanish, and achieved a prodigious success. "Inoculation ribbons" were manufactured, but people still hesitated to have themselves inoculated, although inoculation became the fashion. The example was set by the Chevalier de Chastelux, and next by the Duke of Orleans, whose son and daughter were inoculated by Tronchin in 1756, by Turgot, master of requests, and by the Marquis de Villequier, as also by certain ladies—Madame de Walle, the Countess de Forcalquier, and the Marquise de Villeroy. In the discussion that followed the reading by La Condamine of his second paper before the Academy of Sciences in 1758, the *anti-inoculationists* appealed to the Deity, the Priests, the Government, and the Courts of Justice.[1] On June 8, 1763, the French Parliament ordered the Faculties of Theology and Medicine to assemble and pronounce a definite opinion on the subject of inoculation; it was, however, "provisionally" enacted that it was "forbidden to practise this operation *in the towns and faubourgs within the jurisdiction of the court.*" There were divisions among the doctors: Délépine spoke against inoculation; Antoine Petit, the President of the Faculty, at a meeting of ninety doctors, spoke in favour of it, and, on moving that "this practice should at least be tolerated," the motion was adopted by fifty-two votes to twenty-six. Subsequent progress was slow; La Condamine wrote his third memoir, and a number of other pamphlets made their appearance.[2]

The opposition finally collapsed. In 1768 the students at the Military School were inoculated, in 1769 those at La Flèche, while 1774 saw the inoculation of Louis XVI. and his brothers. At the Italian Theatre were produced the "Fête of the Inoculation," or the "Fête of the Château," divertissements by Favart. The French Government created a fund for the provision of gratuities for surgeons who performed inoculations in their

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[1] The following are the titles of anonymous pamphlets published in Paris at the time: "Advice to the People on Inoculation," "Examination of Inoculation by a Paris Doctor," "Inoculation Confounded by Common Sense," "Observations on Natural and Artificial Small-pox."

[2] "Letter to M. . . Combating the Historic Memoir of La Condamine" Nancy, 1763. "Inoculation sent back to London by a Paris doctor," &c.

cantons; and several inoculation-houses were established in the environs of Paris by three Englishmen, including one of the brothers Sutton.

Since variolation is undoubtedly efficacious, in spite of severe and fatal cases of artificial variola (about 1 in 300), why is it that, at the end of the eighteenth century, statistics show a recrudescence of mortality from small-pox? According to documents presented by Lettsom to the House of Commons, from 1680 to 1722 (forty-two years), small-pox was responsible for 72 per cent. of the total mortality, while in the following period of the same length (1722 to 1764), which included the first years of variolation, 89 per cent. of the deaths were due to the same cause. Gilbert Blane states, from calculations made by Heberden, that out of every 1,000 persons 70 died from small-pox in the first thirty years of the eighteenth century, and 95 in the last thirty years; he adds that before variolation came into vogue many countries remained free from variola for several decades, but that after the introduction of the practice no country escaped the disease.

The reason is obvious. For inoculation purposes it was necessary to have a supply of variolar virus; in order to combat the most deadly of diseases, a commencement had to be made by preserving the virus with the greatest care. Those who were inoculated did not die, but they disseminated deadly germs on all sides; inoculation should either have been made universal or should have been left severely alone.

The anti-inoculationists might have abandoned all their senseless arguments and retained only this. It is not surprising to find that, after the discovery of vaccine, Jenner and his adherents insistently urged the authorities to prohibit inoculation, and that, even before the era of Jenner, the Parliament of Paris, as the result of a violent epidemic, although it did not issue a general interdict against the practice of inoculation, provisionally forbade it *within the confines of towns and faubourgs*, that is to say, in crowded communities. Variolation, though excellent for individuals, was terribly dangerous to the mass.[1]

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[1] It is the same with regard to sheep-pox, or variola of the sheep, which is inoculated in a precisely similar manner. Inoculation with sheep-pox saves individual animals and even flocks, but it preserves the virus. Variolation would never have been able to stamp out variola.

Inoculation is successful in the individual because variola inoculated in the skin, that is, artificial variola, does not develop in the same way as the natural disease. In the case of the latter, the virus penetrates at once into the humours of the body, passes in its entirety into the blood, becomes deposited at thousands of points in the skin, its chosen soil, and produces the general eruption. In the artificial disease, the virus, which is deposited at one, two, or three points in the skin, develops at these points alone and produces the same number of pustules; after the lapse of a week a little of the virus passes into the humours and is carried by the circulation all over the skin, as in the case of natural variola. This second or secondary eruption, however, is less severe than the single, primitive eruption of natural variola.

The reason is that the natural disease breaks out in fresh soil, while that in which the inoculated eruption occurs has already been modified by the pustules by which it has been preceded. In the interval that elapses between the appearance of the inoculation pustules and the secondary eruption, the system has acquired a certain degree of antivariolar immunity—the poison has already produced a counterpoison. Immunising substances, produced in the first pustules, impregnate the system and protect the non-inoculated regions: immunity extends progressively from the pustules to the entire cutaneous surface. At first the immunity is local; a pustule two days old on the right arm protects the skin in its vicinity, but would not prevent the development of a pustule on the left arm. The immunity, which is slight at the outset, continues to increase; a definite period must elapse before it becomes "absolute." A week after the inoculation it is strong enough to lessen the secondary eruption, but insufficient to prevent it altogether.

In many Mediterranean countries sheep are subject to an infectious and contagious disease, which is so similar to variola that it is called sheep-pox, or variola ovina. As a rule, the disease commences like human variola, after a period of incubation, with a general eruption, and death ensues on the eighteenth day; infection takes place by way of the respiratory (or digestive ?) tract, and the virus spreads through the system and becomes "generalised at the outset." If, however, infection occurs only at a point in the skin, through the animal rubbing

itself against troughs, walls, or infected sheep, the disease begins with a local pustule, does not always become generalised, or, if it does, is of a mild type, and the sheep, half immunised through the first pustule, does not succumb. In the case of sheep-pox there is no known prophylactic, like Jenner's vaccine in that of human variola. All that can be done is *ovination*, which does for sheep what variolation did for human beings before the time of Jenner.

Variolation was killed by vaccination. The first mention of Jenner's discovery in French is to be found in a footnote to the "Traité de l'Inoculation," by Dezoteux and Valentin. Accustomed as we are to-day to vaccination as to the use of fire or the wheel, an effort on our part is necessary in order to understand the suspicious surprise of Jenner's contemporaries.

"Dr. Edward Jenner asserts that all those who have been attacked by cow-pox become permanently exempt from variola, and incapable of contracting it, either by contagion or inoculation. He supports *this singular fact* by twenty-three cases, from which it appears . . . . that those who get cow-pox, or are inoculated with matter from the teats, are much less ill and recover more rapidly than if they had contracted ordinary small-pox, and that besides they never have the eruption. We append this note with the *feeling of distrust* that it is right to entertain when examining novelties, especially in view of the singularity of such observations."

II.

Jenner was born at Berkeley, in Gloucestershire, on May 17, 1749. As a schoolboy he displayed a strong taste for natural history, and devoted his spare time to collecting the nests of dormice and hunting for fossils. His school life over, he was sent to Sodbury, near Bristol, and there apprenticed in surgery and pharmacy to Mr. Ludlow, a surgeon of repute. It was during Jenner's stay at Sodbury that vaccination was first suggested to his observant mind, by a remark made in his presence by a young countrywoman, who came to seek advice. When small-pox was mentioned, the girl at once replied, "I cannot take that disease, for I have had cow-pox." The observation made a deep impression upon Jenner.

On the completion of his apprenticeship Jenner went to London to continue his professional studies under John Hunter, the celebrated physician and anatomist, in whose family he lived for two years. The master was in his forty-second year, the pupil in his twenty-first, and there sprang up between them an abiding friendship, which lasted to the end. The two men were well adapted to understand one another, since both possessed the same simplicity and directness of character, coupled with the same warm heart, lucid intelligence, and fervent love of study. The association had the effect of ripening Jenner's natural gifts. When Jenner told Hunter of the observation made by the countrywoman at Sodbury, and said that he thought that it might perhaps be possible to prevent small-pox by cow-pox, Hunter replied: "Don't think, but try."

In 1771 Captain Cook returned from his first voyage of discovery, and on Hunter's recommendation Jenner, who was still living with Hunter, was employed to arrange and prepare a large portion of the specimens of natural history brought back by the expedition. So ably was the task performed that Jenner was offered the post of naturalist to the second expedition, which set sail in 1772. The offer, however, was declined, for Jenner was bent on returning to Berkeley, partly owing to a feeling of grateful affection for his eldest brother, and partly because of his attachment to the country life of his early youth. We now find him leading the life of an energetic and popular country doctor, going his rounds on horseback; on one occasion having to be out in a very severe snowstorm, he nearly succumbed to the cold. He is reported to have said in a joke that doctors really ought to follow the example of workmen, and teach justice to their employers by declaring a "general strike."

An observer by nature, Jenner continued his studies and reflections, advancing new views on angina pectoris, cardiac affections, and ophthalmia, corresponding with Hunter, preparing dissections, and making investigations upon the subject of hibernation. Hunter proposed that he should be his assistant in London, but he declined to leave the country. He sent to the Royal Society a paper on the habits of the cuckoo, and among other subjects which occupied his attention were the cause of tubercle of the lungs, the affections of the lymphatic system and

the diseases of animals. Jenner's leisure hours were devoted to his family, to walking, music and poetry; his verses, many of which have been preserved for us by his biographer, are the unpretentious effusions of a man who preferred the culture of the mind to cards.[1]

Through Jenner's instrumentality there was founded a society of local medical men, the names of the members of which, such as Parry, Hicks, Ludlow, Matthews, and Paytherus are enshrined in the history of vaccination. The meetings of the society were chiefly held at the "Fleece Inn," at Rodborough, and at the dinner that regularly followed the formal communication of papers and observations Jenner contributed in no small degree to the mirth of the party. Jenner also belonged to another society, which met chiefly at the "Ship Inn," at Alveston, near Bristol; here he repeatedly referred to the subject of cow-pox, and the popular idea that those who had had this disease were insusceptible to small-pox. His medical brethren, however, were indifferent and sceptical, regarding the idea as a vague notion of no value, "especially as most of them had met with cases in which those who were supposed to have had cow-pox had subsequently been affected with small-pox." Had Jenner been less of an enthusiast he might have been discouraged; instead, he continually reverted to the subject of cow-pox, his fixed idea, until his colleagues became exasperated and threatened to expel him if he persisted.

Twenty years of observation and study prepared the way for the publication of the "Inquiry into the Causes and Effects of the Variolæ Vaccinæ," the first edition of which appeared in June, 1798. The discovery having at length been made, it was now necessary to defend and extend the practice of vaccination, and Jenner's whole time was occupied with journeys to London, visits, discussions, correspondence, and inoculations. When, however, he was promised an income of £10,000 a year if he would set up in practice as a vaccinator in London, he declined to leave his native place. "Shall I," he wrote to a friend on September 29, 1798, "who even in the morning of my days

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[1] "Address to a Robin"; "Signs of Rain"; "On Seeing an Old Man Mowing"; "Dialogue between Minx the Cat and Tartar the Terrier Dog"; "Berkeley Fair," &c.

sought the lowly and sequestered paths of life, the valley, and not the mountain ; shall I, now my evening is fast approaching, hold myself up as an object for fortune and fame ? Admitting it as a certainty that I obtain both, what stock should I add to to my little fund of happiness ? " Writing to his friend Gardner with reference to his new house at Berkeley, he remarked that he felt his mind "as *cottagish* as ever."[1] He was certainly not rich, and was still obliged to practise his profession for a livelihood ; the post was dear, and his correspondence very expensive. On two occasions the House of Commons voted him sums of money by way of reward (£10,000 in 1802, and £20,000 in 1807), although in both cases by small majorities. Yet, when easy circumstances and renown came to him, they were soon followed by private sorrows, and he lost (in 1810 and 1815), in all probability from pulmonary tuberculosis, his son Edward and his wife, to whom he was tenderly attached. In one of his letters to Gardner, he observes that small sorrows are swallowed up and blotted out by a great grief—the remark of a wise but certainly not an unfeeling man.

Jenner was the possessor of a simple, healthy, positive, and practical nature, and of a calm energy of character which nothing daunted. He was a true scientist, who, living in close communion with Nature and loving her, received from her the secret that was destined to save millions of human lives ; conscious of his own worth, he yet retained, as his fame increased, a noble simplicity. Faithful to his friendships, he cultivated the society of his fellows, often in a playful mood like those who are truly serious. Under the sturdy calm of his outward demeanour there lay a keen sensibility ; from the very beginning he saw the importance of his discovery, and the immensity of the horizons that it opened up ; he was stirred and at times almost intoxicated by the prospect, but never vain. Between joy and apprehension, he experienced something akin to anguish in the years 1796 and 1797, when the

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[1] ". . . . I feel my mind as *cottagish* as ever ; and when you see my habitation finished you will allow me to be quite as retired and countrified a yourself. Whether a man sits on a sofa or a bench, dines off a plate or a trencher, it does not, according to my ideas, make much difference. Still I think his mind may delight in the very opposite to that which mankind in general run after."

first vaccination was performed from arm to arm, and James Phipps, a healthy boy of some eight years of age who was selected for the experiment, was tested with variolous virus several months after having been vaccinated. "While the vaccine discovery was progressive," wrote Jenner, "the joy I felt at the prospect before me of being the instrument destined to take away from the world one of its greatest calamities, blended with the fond hope of enjoying independence and domestic peace and happiness, was often so excessive that, in pursuing my favourite subject among the meadows, I have sometimes found myself in a kind of reverie."

Jenner was gifted with a lively imagination, and intuition gave an impulse to his arguments and experiments. Those to whom his remarks were addressed sometimes found his language "too figurative," and his excellent biographer Baron does not hesitate to declare that "those who could not penetrate below the surface" deemed him "rather visionary." In a discussion on the possibility of earthworms being useful to man, the illustrious Sir Humphrey Davy thought that Jenner "was sometimes carried too far by the remoteness of his analogies."

Towards the end of his life his fame was established beyond dispute ; opposition declined, and the learned societies of the world regarded it as an honour to be allowed to add the name of Jenner to their rolls. The Institute of France made him a corresponding member in 1808. At this time of universal war, when successive coalitions were formed by England against France under Napoleon, Jenner's signature to a passport was considered a sufficient guarantee, and he had to sign many such documents. On several occasions, a letter from him sufficed to obtain from the Emperor the release of Englishmen detained on the Continent ; yet, when an attempt was made to procure a similar favour on behalf of a French prisoner of war, we are told by Baron that "unhappily, Jenner's influence with the British Government was not equal to that which he enjoyed with the Court of France." The task of presenting Jenner's petitions to the Emperor devolved upon Baron Corvisart, the Imperial physician. On one of these occasions, when Napoleon was about to refuse the request, the Empress Joséphine mentioned Jenner's name, whereupon

"the Emperor paused for an instant, and exclaimed, 'Jenner! ah, we can refuse nothing to that man.'"

It was in the following terms that Jenner besought the National Institute of France to intercede on behalf of Lord Yarmouth, who was detained in France with his family. "Gentlemen," he wrote, "pardon my obtruding myself on you at this juncture. The Sciences are never at war. Peace must always preside in those bosoms whose object is the augmentation of human happiness . . ." The allied sovereigns, who visited London in 1814, after the close of the war, paid their respects to Jenner.

This Englishman had in him the fibre of one of Plutarch's Greeks. His excellent biographer Baron,[1] who saw him for the first time in 1808, praises the simplicity of his manner, and the "familiar tone" and "perfect sincerity" of his language.

Though more than twenty years have elapsed," he writes, "since this interview took place, I remember it, and all its accompaniments, with the most perfect accuracy. He was dressed in a blue coat, white waistcoat, nankeen breeches, and white stockings. All the tables in his apartment were covered with letters and papers on the subject of vaccination, and the establishment of the National Vaccine Institution. . . . He spoke with great good humour also of the conduct of the anti-vaccinists, and gave me some pamphlets illustrative of the controversy then carrying on. . . . Our second interview took place in his own house at Berkeley. His eldest son Edward was then lying in the last stage of pulmonary consumption. . . . Some years after, he wept when he talked to me of this son. . . ."

"Dr. Jenner's personal appearance to a stranger at first sight was not very striking; but it was impossible to observe him, even for a few moments, without discovering these peculiarities which distinguished him from all others. This individuality became more remarkable the more he was known;

[1] "The Life of Edward Jenner, M.D., LL.D., F.R.S., &c., with Illustrations of his Doctrines, and Selections from his Correspondence," by John Baron, M.D., F.R.S. Two vols. (London: Henry Colburn, Great Marlborough Street, 1838.)

and all the friends who watched him longest, and have seen most of his mind and of his conduct, with one voice declare that there was a something about him which they never witnessed in any other man. The first things that a stranger would remark were the gentleness, the simplicity, the artlessness of his manner. There was a total absence of all ostentation or display ; so much so, that in the ordinary intercourse of society he appeared as a person who had no claims to notice. He was perfectly unreserved, and free from all guile. He carried his heart and his mind so openly, so undisguisedly, that all might read them. . . . He seemed to have no secrets of any kind ; and, notwithstanding a long experience with the world, he acted to the last as if all mankind were trustworthy, and as free from selfishness as himself. He had a working head, being never idle, and accumulated a great store of original observations. These treasures he imparted most generously and liberally. Indeed his chief pleasure seemed to be in pouring out the ample riches of his mind to everyone who enjoyed his acquaintance. . . . His later days were occasionally gladdened by the studies and pursuits of his youthful years. Geology, which had made such rapid strides since he commenced his enquiries, continued to interest him to the last."[1]

In spite of the simplicity of his nature, Jenner was by no means devoid of dignity. "In the drawing-room at St. James's he chanced to overhear a noble lord, who was high in office, mentioning his name, and repeating the idle calumny which had been propagated concerning his own want of confidence in vaccination. . . . He, with the greatest promptitude and decision, refuted the charge and abashed the reporter. His person was not known to the noble lord, but with entire composure he advanced to his lordship, and looking fully in his face, calmly observed 'I am Dr. Jenner.' The effect of this well-timed rebuke was instantaneous. The noble lord, though 'made of sterner stuff' than most men, immediately retreated, and left Jenner in possession of the field."

It was not always his professional brethren who gave him

[1] Pasteur always regretted not having found time to resume his early studies in crystallography.

the greatest support, and in fact on more than one occasion he had to suffer for their actions. During the controversial period he frequently preferred the assistance of laymen to that of doctors, because the former obediently followed his instructions, while the latter were always desirous of introducing some innovation of their own.

Among the sayings of Jenner preserved for us by his biographer is a reply to a question by Charles James Fox, who, while staying at Cheltenham, frequently met Jenner. "Pray, Dr. Jenner," said Fox one day, "tell me of this cow-pox that we have heard so much about: What is it like?" "Why," replied Jenner, "it is exactly like the section of a pearl on a rose-leaf."

Jenner had a slight attack of apoplexy in August, 1820, but recovered, and his intellectual activity continued unimpaired. His thoughts were still fixed on the great work of his life. In a note on the back of a letter a few days before his death, he wrote: "My opinion of vaccination is precisely as it was when I first promulgated the discovery." A second attack of apoplexy occurred on January 25, 1823, to which Jenner succumbed on the following day, in his seventy-fourth year. The suggestion of a public funeral in Westminster Abbey was not adopted, and Jenner's remains were deposited in a vault in Berkeley Church, by the side of those of his wife.

A country doctor and fervent believer in inoculation, Jenner observed that many of those whom he was required to inoculate "resisted every effort to give them the small-pox." "These patients," he writes, "I found had undergone a disease they called the cow-pox, contracted by milking cows affected with a peculiar eruption on their teats. On inquiry, it appeared that it had been known among the dairies from time immemorial, and that a vague opinion prevailed that it was a preventive of the small-pox. This opinion I found was, comparatively, new among them; for all the old farmers declared they had no such idea in their early days—a circumstance that seemed easily to be accounted for, from my knowing that the common people were very rarely inoculated for the small-pox, till that practice was rendered general by the improved method introduced by the Suttons; so that the

working people in the dairies were seldom put to the test of the preventive powers of the cow-pox."[1]

Writing of the cow-pox in 1798, Jenner said: "It appears on the nipples of the cows in the form of irregular pustules. At their first appearance they are commonly of a palish blue, or rather of a colour somewhat approaching to livid, and are surrounded by an inflammation. These pustules, unless a timely remedy be applied, frequently degenerate into phagedenic ulcers, which prove extremely troublesome. The animals become indisposed and the secretion of milk is much lessened. Inflamed spots now begin to appear on different parts of the hands of the domestics employed in milking, and sometimes on the wrists, which quickly run on to suppuration, first assuming the appearance of small vesications produced by a burn. . . . The system becomes affected, the pulse is quickened; shiverings, succeeded by heat, general lassitude and pains about the loins and limbs, with vomiting, come on. . . . No eruptions on the skin have followed the decline of the feverish symptoms in any instance that has come under my inspection, one only excepted. . . ."[2]

We see, then, that cow-pox scarcely ever produces a general eruption, as small-pox does when inoculated.

From the very beginning Jenner encountered the objection that appeared decisive to his Gloucestershire colleagues; people who had had cow-pox subsequently contracted small-pox. Jenner continued his observations and discovered that, in these negative cases, the patients had suffered, not from true cow-pox, but from other disorders which resembled it so closely that the popular mind did not distinguish between them; *there was a true and a false vaccine.*

"In the course of the investigation of this subject, which, like all others of a complex and intricate nature, presented many difficulties, I found that some of those *who seemed to have undergone the cow-pox*, nevertheless, on inoculation with small-pox, felt the influence just the same as if no disease had been

[1] "On the Origin of the Vaccine Inoculation," pp. 1-2 (London: D. N. Shury, 1801).

[2] "An Inquiry into the Causes and Effects of the Variolæ Vaccinæ, &c." (1798).

communicated to them by the cow. This occurrence led me to inquire among the medical practitioners in the country around me, who all agreed in this sentiment that the cow-pox was not to be relied upon as a certain preventive of the small-pox. This for a while damped, but did not extinguish, my ardour; for as I proceeded I had the satisfaction to learn that the cow was subject to some varieties of spontaneous eruptions upon her teats; that they were all capable of communicating sores to the hands of the milkers; and that whatever sore was derived from the animal was called in the dairy the cow-pox. Thus I surmounted a great obstacle, and, in consequence, was led to form a distinction between these diseases, one of which only I have denominated the *true*, the others the *spurious*, cow-pox, as they possess no specific power over the constitution."[1]

A fresh objection, which assumed an even more embarrassing form, however, presented itself; people who had received *the true vaccine* subsequently proved susceptible to small-pox.

"There were not wanting instances to prove that when the true cow-pox broke out among the cattle at a dairy, a person who had milked an infected animal, and had thereby apparently gone through the disease in common with others, was liable to receive the small-pox afterwards. This, like the former obstacle, gave a painful check to my fond and aspiring hopes; but reflecting that the operations of Nature are generally uniform, and that it was not probable the human constitution (having undergone the cow-pox) should in some instances be perfectly shielded from the small-pox, and in many others remain unprotected, I resumed my labours with redoubled ardour. The result was fortunate; for I now discovered that the virus of cow-pox was liable to undergo progressive changes from the same causes precisely as that of small-pox; and that when it was applied to the human skin in its degenerated state it would produce the ulcerative effects in as a great a degree as when it was decomposed, and sometimes far greater; but having lost *its specific properties* it was incapable of producing that change upon the human frame which is requisite to render it unsusceptible of the variolous contagion. . . ."[2]

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[1] "Origin of the Vaccine Inoculation," pp. 2-3.
[2] *Ibid.*, pp. 3-4.

The failures, as Jenner found, were due to the infection having been contracted from a pustule in a too advanced stage, so that the "leaven" was enfeebled or dead. We have since learnt the reason why these advanced pustules continued to be infectious; they contained the microbes that ordinarily cause suppuration, and give rise to boils, phlegmons, and erysipelas. Jenner's non-vaccinating pustules are explained by the staphylococcus and streptococcus of Pasteur.

"During the investigation of the casual cow-pox," Jenner writes, "I was struck with the idea that it might be practicable to propagate the disease by inoculation, after the manner of the small-pox, first from the cow, and, finally, from one human being to another." This was done, and, in modern phraseology, Jenner made an experimental transmission of the vaccine of the cow to man, followed by a series of transmissions from one human being to another.

These experiments were inspired by intuition. Thinking that our diseases may come to us from domestic animals, kept in the house or its precincts; that a virus may pass from the cow to man; that in the course of ages virus or "leaven" has succeeded in migrating from one species to another, in adapting itself to different species, and in producing different kinds of virulent types, such were the steps in Jenner's great discovery. His conception was in advance of his time and even of what he accomplished; the grandeur of it was not fully understood until the epoch of Pasteur, that second great pioneer, who again brought it into prominence by introducing "vaccination" for chicken cholera and anthrax. When the etiology of tuberculosis was explained by Villemin and Koch, they repeated in the case of this disease Jenner's experiments on vaccine.

The names of little Meister and the shepherd-boy Jupille, the first children inoculated by Pasteur against hydrophobia, are rightly kept in remembrance. Let us also recall the names of Jenner's first subjects. Sarah Nelmes, a dairymaid, who was attacked with cow-pox in May, 1796, furnished the virus with which Jenner inoculated the arm of James Phipps, a boy aged 8. On July 1 of the following year Phipps was inoculated with variolous virus. "I could scarcely persuade myself the patient was secure from the small-pox," writes Jenner. "How-

ever," he continues, "on his being inoculated some months afterwards, it proved that he was secure. This case inspired me with confidence, and as soon as I could again furnish myself with virus from the cow I made an arrangement for a series of inoculations. A number of children were inoculated in succession, one from the other, and after several months had elapsed they were exposed to the infection of the small-pox; some by inoculation, others by variolous effluvia, and some in both ways, but they all resisted it. . . . The distrust and scepticism which naturally arose in the minds of medical men on my first announcing so unexpected a discovery has now nearly disappeared."[1]

It must not be forgotten that at that time great services were rendered by variolation. The immense advantage of vaccination, however, is that it scarcely ever causes complications, and never leads to generalization, a secondary eruption, or any risk. "It is an excess in the number of pustules which we chiefly dread in the small-pox; but in the cow-pox the number of pustules never exceeds that of the punctures."

Jenner's opponents brought forward cases in which the vaccinal pustules were accompanied by high fever and serious symptoms. We now know that in these cases the pustules had been produced by impure vaccine, containing the micro-organisms of suppuration in large quantities; Jenner was unacquainted with these microbes, but he furnished the explanation of the fact, pointing out that "the most material indisposition, or at least that which is felt most sensibly, *does not arise primarily from the first action of the virus on the constitution, but that it often comes on, if the pustule is left to chance, as a secondary disease.*" "As the cases of inoculation multiply," he writes, "I am more and more convinced of the extreme mildness of the symptoms arising merely from the primary action of the virus on the constitution, and that these symptoms, which (as in the accidental cow-pox) affect the patient with severity, are entirely secondary, excited by the irritating processes of inflammation and ulceration. . . ."

Later on attention was concentrated on obtaining virus in the purest possible condition. The great improvement was

[1] "Origin of the Vaccine Inoculation," pp. 6-7.

asepsis, but for the complete solution of the problem we must await the discovery of a method of making cultures of the vaccinal virus in broth. Jenner instinctively advised asepsis, and censured medical men for employing, for the purpose of *inoculation*, virus kept in a phial without proper precautions. One practitioner, he tells us, "frequently preserved the variolous matter intended for his use on a piece of lint or cotton, which, in its fluid state, was put into a vial, corked, and conveyed into a warm pocket : a situation certainly favourable for speedily producing putrefaction in it. In this state (not unfrequently after it had been taken several days from the pustules) it was inserted into the arms of his patients and brought on inflammation of the incised parts, swellings of the axillary glands, fever, and sometimes eruptions. But what was this disease? Certainly not the small-pox. . . ."

Jenner was still imbued with the idea of "pure virus" when he explained the complications that occurred in 1799, at the Small-pox Hospital in London, under Dr. Woodville, physician to the hospital. Among a large number of children vaccinated there were a few cases of severe eruption, and one child was said to have died. Vaccination in a hospital containing small-pox patients was performed under peculiar conditions, the fact being that variola and vaccinia were closely associated within the hospital walls. As is well known, the great difficulty in experimenting with the virus of these two diseases is to keep them uncontaminated by each other. At this period, when variolation was in vogue and vaccination in its infancy, mistakes were sometimes made in charging the lancets. The virus of both kinds was also provided for use on pieces of dry thread, which were then inserted into small incisions in the skin ; on one occasion an apothecary noticed that a medical man had impregnated the whole of a batch of threads with variola instead of vaccine. The clamour that arose in connection with one case of failure in vaccination irritated Jenner, who wrote that the public knew "no more of the laws of the animal economy than those of Lycurgus." His one idea now was to get variolation prohibited, and in 1807 he made an unsuccessful attempt to induce the Government to take action in the matter. Bills for the regulation of small-pox inoculation, which were subsequently introduced into both Houses of Parliament, failed

to receive support, and the practice of variolation was long continued at the Small-pox Hospital in London.

In 1811, the Honourable Robert Grosvenor, who some ten years before had been vaccinated by Dr. Jenner himself, had a severe attack of small-pox. The case produced a great sensation among medical men and the public generally, though there can be little doubt that the patient's ultimate recovery was due to the previous vaccination ; the necessity for *revaccination*, to which the case pointed, was not yet realized.

The progress of vaccination was rapid, the foundation in London of the first Vaccine Institution, under the patronage of His Royal Highness the Duke of York, which took place in 1800, was followed in 1803 by that of the Royal Jennerian Society. Thirteen stations for vaccination were opened in the capital ; 12,288 persons were vaccinated in eight months, and 19,352 doses of vaccine were despatched to the provinces and abroad. The number of deaths from small-pox, which had averaged 2,018 per year for the preceding years, fell from 2,409 in 1800 to 1,173 in 1803, and 622 in 1804.

While staying at Cheltenham, Jenner offered gratuitous vaccination to all poor people who chose to apply for it at stated times ; the majority of parents did so, "bringing their children in great numbers both from the town and the adjoining parishes." In the summer of 1800 the inhabitants of one parish, who previously had always been refractory, followed the example of their neighbours, and Jenner naturally "wished to know by what means they had become converts to the new inoculation. He found that arguments of a very authoritative nature had brought about the change. The small-pox, in the course of the preceding year, had been introduced into the parish and proved extremely fatal ; but it was not this circumstance, nor yet the security of those who had been vaccinated in the adjoining parishes, that brought cow-pox inoculation into favour. The cost of coffins for those who were cut off by small-pox proved burdensome to the parish ; the churchwardens, therefore, moved by this argument, effectually exerted their authority and compelled the people to avail themselves of Dr. Jenner's kind offer."

Opposition to an innovation was not surprising, but Jenner also experienced the sting of calumny. It was currently

reported that, instead of vaccinating his son Robert when in danger of small-pox, he had inoculated the boy with the virus of the disease itself, so that he had small confidence in his own vaccine. The actual facts, however, were very different. While Jenner was staying with his family at Cheltenham, a friend entered the house and, picking up his child, remarked that he "had just left a family labouring under small-pox." Jenner immediately exclaimed, "Sir, you know not what you are doing. That child is not protected. He was vaccinated, but the infection failed." Believing that the natural small-pox would certainly follow this exposure, he was greatly distressed and alarmed. He had no vaccine matter. He resolved, therefore, to adopt the next best expedient, and immediately had the child inoculated with the small-pox virus.

At the Royal Military Asylum, where 1,100 soldiers' children were permanently maintained, there was but *one* death from small-pox from 1803 to 1811, and not a single one at the Foundling Hospital. Unhappily, however, it was not long before vaccination was again neglected in England ; the mortality from small-pox in 1825 was only equalled by that in the years 1779 and 1781, but it is estimated that in 1825, had it not been for vaccination, there would have been 4,000 victims instead of 1,289.

The matters that occupied Jenner's attention were not exclusively of a practical order. He set himself to discover the origin of the virus of the cow, and came to the conclusion that the original malady is a disease of the horse, known as *grease*. If man usually becomes infected by contact with the cow, he also does so by contact with the horse, and as a matter of fact, Jenner maintains, the virus is carried by man from the horse to the cow. Thus we have three kinds of vaccinal virus —the *horse-pox* or virus of the horse, the *cow-pox* or vaccine of the cow, and the *man-pox*, which is the same virus implanted in human beings. That of man comes from the horse or the cow, that of the cow comes from the horse ; but since transmission to man appears to take place more readily from the cow than from the horse, Jenner thought that, in order that the original virus of the horse may become adapted to our species, a preliminary *passage* through the cow is indispensable.

"The active quality of the virus from the horses' heels is

greatly increased after it has acted on the nipples of the cow, as it rarely happens that the horse affects his dresser with sores, and as rarely that a milkmaid escapes the infection when she milks infected cows."

This belief in the equine origin of vaccine, to which Jenner was strongly attached, was keenly contested by his contemporaries, but has been confirmed by subsequent observations. In Jenner's view the virus of all three diseases, including small-pox, is essentially the same, and this is why one confers immunity to another. Jenner was the first to enunciate the conception of the variability of virus, the influence of the animal host, and the modifications produced by *passages* through particular species. He took pleasure in showing that Nature's methods are simple.

"In my first publication on this subject," he writes, "I expressed an opinion that the small-pox and the cow-pox were the same diseases under different modifications." "The source of the infection is a peculiar morbid matter arising in the horse." "May it not then be reasonably conjectured that the source of the small-pox is morbid matter of a peculiar kind, generated by a disease in the horse, and that accidental circumstances may have again and again arisen, still working new changes upon it, until it has acquired the contagious and malignant form under which we now commonly see it making its devastations amongst us? . . . The same question will apply respecting the origin of many other contagious diseases which bear a strong analogy to each other."

Nowadays it is considered that there is no stronger proof of the relationship or identity of two forms of virus than the ability of the one to confer immunity to the other.

The earliest promoters of vaccination on the Continent were De Carro in Vienna (1798), and Sacco in Italy. Sweden, Denmark, the German States, and Austria (1809), made vaccination compulsory by law.[1] From the very beginning of the nineteenth century vaccination made its way into Venezuela

[1] In the District of Anspach (300,000 inhabitants) there were only four deaths from variola in 1809, and not a single one from 1809 to 1818; in Wurtemberg, however, there were very severe epidemics from 1814 to 1818. From 1777 to 1799 there had been on an average 500 deaths per year in Anspach, and

and the Spanish colonies in America, but its introduction into France was retarded by wars. On May 11, 1800, there was founded in Paris, by the Institute and the School of Medicine, a Central Committee for the study of vaccinia.[1] The first trials were made at the Salpêtrière under Dr. Pinel with virus newly imported from England, and La Rochefoucauld-Liancourt opened a subscription for the purpose of founding a Vaccine Institute in Paris.

Societies with similar ends in view were founded at Reims, Amiens, Rouen, Marseilles, Bordeaux, and Brussels, and in 1800 Count de Laroque translated Jenner's "Inquiry." The functions of the Central Committee were taken over by the Royal Academy of Medicine, established in the reign of Louis XVIII. (decree of December 20, 1820), and Bousquet was the first Director of the Vaccination Department of the Academy. "Besides the children from the town," wrote Bousquet, "I receive those from the hospitals who, by one of those compensations without which society could not continue to exist, preserve the fluid vaccine indefinitely."

Vaccination was performed from arm to arm, with the result that after some years there came into existence a "humanized" vaccine, a virus which, originating in the cow, was perpetuated in the human species. Even in 1801 there was an impression that the antivariolous efficacy of the vaccine was attenuated, and about 1815 it was found necessary to renew the vaccine in all countries and to take it from its natural source, the teat of the cow. The new vaccine produced fine pustules, similar to those which Jenner had described, after an incubatory period of the same length ; the pustules from humanized virus appeared after a shorter period of incubation and lasted longer, but were smaller in size. Cases of horse-pox and cow-pox were sought for and made use of everywhere.

It was noticed that vaccinal immunity might not continue

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there were 1,609 deaths in 1800. In Prussia, in spite of an extension of territory and an increase in the population, the death-rate from small-pox fell from an average of 40,000 to 3,000 (1817). About the latter year the death-rate was 1 per 7,204 inhabitants in Prussia, and 1 per 4,518 in France.

[1] The members of the Committee were Pinel, Thouret, Leroux, Parfait, Monjenot, Guillotin, Doussin-Dubreuil, Marin and Salmade.

indefinitely, and that about ten years after the first vaccination a revaccination frequently gave a positive result ; further, it was found that it was necessary, especially when an epidemic was threatening, to revaccinate at about the ages of 30 and 40. Revaccination, which has been compulsory in Germany since 1874, only became so in France by the law of February 15, 1902, which deals with the protection of the public health.

To return once more to the subject of humanized vaccine ; it was found that while this continued to decrease in strength, those who were revaccinated were less sensible to the action of the vaccine ; the virus available was less efficacious and the subjects were more resistant. This, however, was not the only drawback in connection with arm-to-arm vaccination ; it often happened, as shown by sad examples in medical records, that such vaccine was a vehicle for infectious disease. In 1865, vaccine supplied by the Royal Academy of Medicine infected eleven persons with syphilis, and there were other vaccinal "epidemics" of the same disease. Vaccination was also accused of disseminating scrofula and rickets, and of debilitating the race.

It was therefore evident that the operation must be performed with virus from the cow, but cases of natural cow-pox are rare. To transmit vaccine from cow to cow, from teat to teat, using nothing but the teats, was scarcely to the interest of the dairy farmer. The success of *animal vaccination*, that is to say, vaccination with vaccine which has not been passed through the human body, dates from the inception of the idea of producing pustules by the hundred on the flanks of a calf. The method, which was introduced into France by Lanoix and Chambon, was already employed at Reims and Naples at the beginning of last century.[1] The vaccigenous calf has become

[1] In 1801 Husson and Tissier, of Reims, transmitted vaccine from man to the cow in order to increase its activity, and in 1804 Troja introduced the same practice at Naples, with the same end in view. *Animal vaccination*, as the definitive method, was established by Gennaro Galbiati, a pupil of Troja, who in 1810 published his memoir, "On the Inoculation of Vaccine by Means of Pus derived directly from the previously Inoculated Cow." At the Medical Congress held at Lyons in 1864, when Dr. Alexandre Viennois proposed that human vaccine should be abandoned in favour of that from the horse or cow, Dr. Palasciano, a surgeon of Naples, described the method that had long been in use

a popular institution in France, and, when vaccinations and revaccinations are in progress, is to be seen in lying-in hospitals, schools, barracks, and even the public squares.

A healthy calf is selected for the purpose a few weeks after being taken from the cow, and is scientifically examined to make sure that it is free from tuberculosis and glanders. It is kept under observation for a fortnight, placed in a loose-box with cemented walls and floor, and provided with carefully chosen bedding, which is frequently renewed. A few hours before inoculation the animal's flanks are clipped, shaved, and washed with soap and water ; the abdomen and rump, which are more liable to become soiled, are not treated in this way. For the actual inoculation, the operator makes in the epidermis by means of a lancet vertical incisions or scarifications, about a centimetre and a half in length and three or four centimetres apart, arranged quincuncially ; blood should not be made to flow, and scarcely even should the scratches lead to the oozing of a few small spots. A brush charged with vaccine is passed over each incision, and the animal is returned to its stall, after being fitted with a collar which prevents it from bending its neck in order to lick itself. On each of the incisions a pustule develops, the total number of pustules being about one hundred and fifty.

On the fifth day, when the collection is made, each pustule is seized between the tips of a pair of long sterilized forceps ; the crust is then removed and thrown away, and the derm thus exposed is slowly scraped with a broad-bladed scalpel ; any doubtful looking pustules are left untouched. The fresh vaccinal pulp obtained by the scraping process is received in a sterilized vessel. The calf, having thus been duly vaccinated and rendered immune, is of no further use, and, being a selected animal, is handed over to the butcher.

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in his city. Chambon and Lanoix studied the system at Naples itself, and, in December, 1864, organized in Paris the first regular vaccination service with calf lymph.

Chambon set himself to find Galbiati's memoir, which was said to be undiscoverable, and was fortunate enough to meet with a copy, of which he has published a French translation, with a preface whence these notes are extracted ("Mémoire de Gennaro Galbiati sur la Vaccination Animale à Naples, 1810." Paris : Rueff, 1906). Thanks are due to Dr. Chambon for the services rendered by him to the practice and history of vaccination.

The ideal form of vaccination is to transfer the vaccine straight from the calf to the human skin, but this is not practicable everywhere, and supplies of vaccine have to be sent into the country and to the colonies. Fresh vaccine very rapidly loses its efficacy, and it was therefore necessary to seek for means of preserving it. In a semi-fluid condition it was preserved between glass plates or in capillary tubes, while, in a dried state, it was kept on threads, linen, plates of glass, lancets, ivory blades, goose quills, and strong thorns like those of the rose or Indian fig-tree. In a dry condition the virus keeps longer than when moist, but in the end the efficacy of all vaccine is destroyed by time, light, and especially heat.

Virus which is kept in a fluid state becomes full of microbes ; inoculation in the calf results in an animal culture, which by dint of precautions can be rendered clean, but is not a pure culture. The germs collected in scraping the pustules of the calf are hardly ever pathogenic, but a few virulent germs are sufficient to produce an abscess or phlegmon. Though the fresh pulp be poor in pathogenic microbes, these may multiply when the pulp is kept, and the question was how to purify it.

For this purpose the vaccine was mixed with bodies which prevent the development of microbes without destroying the vaccinal virus, and among the agents tried were chloroform and toluene. Leoni rendered a great service to vaccination when he conceived the idea of employing glycerine, which both purifies and preserves the vaccine. The fresh pulp collected from the calf is pounded as finely as possible, and mixed with an equal weight of neutral glycerine ; the resultant product is glycerinated lymph, which is furnished to vaccinators in hermetically sealed capillary tubes, kept at a low temperature and protected from light. In glycerinated lymph the foreign microbes are killed in forty to fifty days, without detriment to the efficacy of the vaccine.

The most favourable time for inoculation is when the lymph is most sterile and as fresh as possible ; this period varies with the season, climate, and conditions of temperature and light. Before a tube of vaccine is supplied for use, the batch to which it belongs is tested by inoculating a sensible animal, such as a mouse, a guinea-pig, or rabbit. The eye of the latter furnishes the most delicate test ; on the transparent

integument of the cornea active vaccine produces an opaque spot, which is a small vaccinal vesicle. A still better method is to inoculate a child with the glycerinated (*i.e.* purified) vaccine, which is the best means of testing its specific value without any danger.

In hot countries, such as our colonies in Asia and Africa, the production and preservation of vaccine is a difficult problem. The buffalo, goat, and rabbit are all employed, but owing to the temperature only yield small pustules. Glycerinated lymph sent out from home soon becomes inactive, and in order to keep it at a low temperature use is now made of the double-walled flasks, that enclose a vacuum and are employed to contain liquid air; the little tubes of vaccine are immersed in a freezing mixture, which can be renewed as required. In the Tropics vaccinal immunity appears to be less pronounced and less permanent than in temperate climates.

In man the vaccinal pustule normally commences to develop on the fourth day after inoculation; the crust does not fall off until the twentieth day. When the vaccine does not "take," the reaction, as evinced by itching and redness, occurs almost immediately, and it may be asked whether this is of vaccinal origin. It was formerly thought that the system responded to vaccination only positively or negatively—that it was a case of all or nothing: nowadays it is believed that there are all degrees in the activity and efficacy of the pustule, and that the subject reacts more or less. Thus a semi-successful vaccination might strengthen an immunity enfeebled by time. As Jenner himself observed: "The human body is always more or less susceptible to the infection of cow-pox; but a second attack is usually very slight."

III.

The story of vaccination presents a contrast which is unique in medical science: in practice the matter is settled, but theoretically it is still an open question and full of mystery. There has never been, and doubtless there never will be so wonderful a discovery, and, owing to the simplicity of the means employed, the certainty of the results, and the universality of the success attained, we are justified in regard-

ing vaccination as the typical preventive medicine. There is little difficulty, therefore, in understanding how it was that Pasteur, after thirty years of experimental research and discoveries resulting therefrom, was fascinated by this instance of brilliant empiricism, this magnificent example of the anticipation of theory by practice. Nevertheless, vaccine still gives rise to a host of questions in microbiology, which await solution.

Variola and vaccinia are virulent contagious diseases, undoubtedly of microbic origin, though in each case the causative agent is unknown. The microbes believed to have been discovered exist only in the imagination, and the supposed protozoon with so complicated a cycle of development, described by Calkins, does not exhibit the characteristics of a living micro-organism. All that can be said is that the microbe of vaccinia is very minute, and capable of passing through the pores of certain filters, similar to those used for drinking water. It is extremely abundant in the vaccinal pulp, which is still very active after being diluted with fifty or a hundred times its volume of water; it belongs to the class of virus termed "invisible microbes," or more accurately "filtering microbes," which are now being studied everywhere. Vaccination reminds us of the Pasteurian treatment for hydrophobia—another triumph of experimental science, consisting in the prevention of another infectious disease, the unknown microbe of which is likewise an infinitely small organism, capable of passing through filters.

No one has yet succeeded in cultivating the virus of vaccinia; the problem presented is one of immense interest, the solution of which would perhaps furnish us with a general method of culture for other kinds of virus, which to-day are non-cultivable. Did we possess pure cultures of vaccine, we might perhaps dispense with the means of culture afforded by the calf, which, though clean, is microbiologically impure.

The vaccinal fluid, or, as Jenner would have said, the vaccinal *leaven*, is derived from the cells of the skin attacked by the virus. Jenner, who was fully aware that this fluid is not pus, compared it to the secretion from a gland. We know that it is not a secretion, but is produced by the disintegration and fusion of the cells occupying the centre of

the vesicle ; everything tends to show that the unknown microbe arises from the diseased cells, and that the vaccinal virus is an intracellular microbe. A similar hypothesis is arrived at as the result of an anatomical study of cancerous tumours. It is true that the different forms of cancer in no way resemble variola and vaccinia, yet there are certain affinities between these two types of disease, and discoveries in connection with the one will be instructive as regards the other.

In Jenner's opinion the virus of variola and that of vaccinia are essentially the same virus, modified by the species of animals through which they pass. His view was that vaccine is a variolar virus attenuated by passage through the cow, or, in other words, that variola is a vaccine adapted to man by passage through the human subject. These ideas have been subjected to the test of experiment, and an attempt has been made to produce vaccine by inoculating animals with variola, that is, to obtain variolo-vaccine. According to the celebrated experiments of the Lyons Commission (1863-65), it is impossible to bring about the transformation of variola into vaccinia in the cow, though others, such as Fischer (of Carlsruhe), in 1890, and Eternod and Haccius, in 1892, claimed to have done so. Even if proof be lacking, Jenner's intuition is confirmed by the best established facts, but it is difficult to achieve in a single generation what Nature has perhaps taken ages to accomplish.

It would appear that in 1905, Dr. Chaumier, of Tours, really succeeded in transforming the virus of sheep-pox into Jennerian vaccine, and Chaumier reminds us that, at the beginning of last century, Sacco and other authors declared that they had obtained vaccinal vesicles by inoculating children with sheep-pox.

In variolation an inoculation was made with the actual virus against which it was desired to protect the individual ; the inoculator produced an artificial attack of variola, usually of a mild type, in order to preserve his patient from the natural disease, which was frequently fatal. In Jenner's vaccination the virus inoculated is different from that of variola ; it is an animal virus, which is employed as a preventive against a human virus. Pasteurian "vaccinations" are different from both variolation

and vaccination; they differ from Jennerian vaccination since the preservative virus is the same as that against which protection is given (the vaccines against anthrax are anthrax microbes); they differ from variolation, because the "variolator" employed variolar virus taken just as it was from a human pustule, while the Pasteurian vaccines are attenuated microbes. The attenuation accomplished under natural conditions through the virus being parasitic on the cow, has been successfully produced by Pasteur in the laboratory, stove, and culture flasks by the action of heat or of chemical substances.

When von Behring was seeking to discover a method of vaccinating cattle against tuberculosis, his efforts were based on Jennerian vaccination, and he hoped that human tuberculosis would serve as a vaccine against the bovine disease. He thought that he could then derive from immunised cattle a remedy which would be efficacious when applied to man, since he believed that human and bovine tuberculosis are caused by the same virus adapted to two different species of animals. Von Behring termed his method the *jennerization* of cattle.

From the remark made by a countrywoman in the presence of the medical apprentice at Sodbury, from a fact of common knowledge developed by a daring conception, has sprung a whole multitude of experiments and ideas. A favourable conjuncture, a mind endowed with more than ordinary perspicacity and stubborn energy in driving an idea into the heads of others—in short, patience and luck, sagacity and will—are ever the constituent elements of genius.

APPENDIX.

AN

INQUIRY

INTO

THE CAUSES AND EFFECTS

OF

THE VARIOLÆ VACCINÆ,

A DISEASE

DISCOVERED IN SOME OF THE WESTERN COUNTIES OF ENGLAND,

PARTICULARLY

GLOUCESTERSHIRE,

AND KNOWN BY THE NAME OF

THE COW POX.

By EDWARD JENNER, M.D., F.R.S., &c.

——Quid nobis certius ipsis sensibus esse potest, quo vera ac falsa notemus.—LUCRETIUS.

SECOND EDITION.

LONDON:

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AND SOLD BY LAW, AVE-MARIA LANE; AND MURRAY AND HIGHLEY, FLEET STREET.

1800.

To the King.

SIR,—When I first addressed the Public on a Physiological subject, which I conceived to be of the utmost importance to the future welfare of the human race, I could not presume, in that early stage of the investigation, to lay the result of my Inquiries at your Majesty's feet.

Subsequent experiments, instituted not only by myself but by men of the first rank in the medical profession, have now confirmed the truth of the theory which I first made known to the world.

Highly honoured by the permission to dedicate the result of my Inquiries to your Majesty, I am emboldened to solicit

your gracious patronage of a discovery which reason fully authorizes me to suppose will prove peculiarly beneficial to the preservation of the lives of mankind.

To a Monarch no less justly than emphatically styled the Father of his People, this Treatise is inscribed with perfect propriety ; for, conspicuous as your Majesty's patronage has been of Arts, of Sciences, and of Commerce, yet the most distinguished feature of your character is your paternal care for the dearest interest of humanity.

I am, Sir (sic)
Sir,
With the most profound respect,
Your Majesty's most devoted
Subject and servant,
Edward Jenner,

Berkeley, *Gloucestershire.*
December 20th, 1799.

The deviation of man from the state in which he was originally placed by Nature seems to have proved to him a prolific source of diseases. From the love of splendour, from the indulgences of luxury, and from his fondness of amusement, he has familiarized himself with a great number of animals, which may not originally have been intended for his associates.

The wolf, disarmed of ferocity, is now pillowed in the lady's lap.[1] The cat, the little tiger of our island, whose natural home is the forest, is equally domesticated and caressed. The cow, the hog, the sheep, and the horse, are all, for a variety of purposes, brought under his care and dominion.

There is a disease to which the horse, from his state of domestication, is frequently subject. The farriers have termed it the *grease.* It is an inflammation and swelling in the heel, from which issues matter possessing properties of a very peculiar kind, which seems capable of generating a disease in the human body (after it has undergone the modification

[1] The late Mr. John Hunter proved, by experiments, that the dog is the wolf in a degenerated state.

I shall presently speak of), which bears so strong a resemblance to the small-pox that I think it highly probable it may be the source of that disease.

In this dairy country a great number of cows are kept, and the office of milking is performed indiscriminately by men and maid-servants. One of the former having been appointed to apply dressings to the heels of a horse affected with the *grease*, and not paying due attention to cleanliness, incautiously bears his part in milking the cows with some particles of the infectious matter adhering to his fingers. When this is the case, it commonly happens that a disease is communicated to the cows, and from the cows to the dairymaids, which spreads through the farm until most of the cattle and domestics feel its unpleasant consequences. This disease has obtained the name of the *cow-pox*. It appears on the nipples of the cows in the form of irregular pustules. At their first appearance they are commonly of a palish blue, or rather of a colour somewhat approaching to livid, and are surrounded by an inflammation. These pustules, unless a timely remedy be applied, frequently degenerate into phagedenic ulcers, which prove extremely troublesome.[1] The animals become indisposed, and the secretion of milk is much lessened. Inflamed spots now begin to appear on different parts of the hands of the domestics employed in milking, and sometimes on the wrists, which quickly run on to suppuration, first assuming the appearance of the small vesications produced by a burn. Most commonly they appear about the joints of the fingers, and at their extremities; but whatever parts are affected, if the situation will admit, these superficial suppurations put on a circular form, with their edges more elevated than their centre, and of a colour distantly approaching to blue. Absorption takes place, and tumours appear in each axilla. The system becomes affected, the pulse is quickened; shiverings succeeded by heat, general lassitude and pains about the loins and limbs, with vomiting, come on. The head

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[1] They who attend sick cattle in this country find a speedy remedy for stopping the progress of this complaint in those applications which act chemically upon the morbid matter, such as the solutions of the vitriolum zinci, the vitriolum cupri, &c.

is painful, and the patient is now and then even affected with delirium.[1]) These symptoms, varying in their degrees of violence, generally continue from one day to three or four, leaving ulcerated sores about the hands, which, from the sensibility of the parts, are very troublesome, and commonly heal slowly, frequently becoming phagedenic, like those from whence they sprung. The lips, nostrils, eyelids, and other parts of the body are sometimes affected with sores; but these evidently arise from their being heedlessly rubbed or scratched with the patient's infected fingers. No eruptions on the skin have followed the decline of the feverish symptoms in any instance that has come under my inspection, one only excepted, and in this case a very few appeared on the arms; they were very minute, of a vivid red colour, and soon died away without advancing to maturation; so that I cannot determine whether they had any connection with the preceding symptoms.

Thus the disease makes its progress from the horse (as I conceive) to the nipple of the cow, and from the cow to the human subject.

Morbid matter of various kinds, when absorbed into the system, may produce effects in some degree similar; but what renders the cow-pox virus so extremely singular is, that the person who has been thus affected is for ever after secure from the infection of the small-pox; neither exposure to the variolous effluvia, nor the insertion of the matter into the skin, producing this distemper.

In support of so extraordinary a fact, I shall lay before my readers a great number of instances; but first it is necessary to observe that pustulous sores frequently appear spontaneously on the nipples of the cows, and instances have occurred, though very rarely, of the hands of the servants employed in milking being affected with sores in consequence, and even of their feeling an indisposition from absorption. These pustules are of a much milder nature than those which arise from that contagion which constitutes the true cow-pox. They are always free from the bluish or livid tint so conspicuous in the

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[1] It will appear in the sequel that these symptoms arise principally from the irritation of the sores, and not from the primary action of the vaccine virus upon the constitution.

pustules in that disease. No erysipelas attends them, nor do they show any phagedenic disposition as in the other case, but quickly terminate in a scab, without creating any apparent disorder in the cow. This complaint appears at various seasons of the year, but most commonly in the spring, when the cows are first taken from their winter food and fed with grass. It is very apt to appear also when they are suckling their young. But this disease is not to be considered as similar in any respect to that of which I am treating, as it is incapable of producing any specific effects on the human constitution. However, it is of the greatest consequence to point it out here, lest the want of discrimination should occasion an idea of security from the infection of the small-pox, which might prove delusive.

Case I.

Joseph Merret, now an under-gardener to the Earl of Berkeley, lived as a servant with a farmer near this place in the year 1770, and occasionally assisted in milking his master's cows. Several horses belonging to the farm began to have sore heels, which Merret frequently attended. The cows soon became affected with the cow-pox, and soon after several sores appeared on his hands. Swellings and stiffness in each axilla followed, and he was so much indisposed for several days as to be incapable of pursuing his ordinary employment. Previously to the appearance of the distemper among the cows there was no fresh cow brought to the farm, nor any servant employed who was affected with the cow-pox.

In April, 1795, a general inoculation taking place here, Merret was inoculated with his family; so that a period of twenty-five years had elapsed from his having the cow-pox to this time. However, though the variolus matter was repeatedly inserted into his arm, I found it impracticable to infect him with it; an efflorescence only, taking on a erysipelatous look about the centre, appearing on the skin near the punctured parts. During the whole time that his family had the small-pox one of whom had it very full; he remained in the house with them, but received no injury from exposure to the contagion.

It is necessary to observe that the utmost care was taken

to ascertain, with the most scrupulous precision, that no one whose case is here adduced had gone through the small-pox previous to these attempts to produce that disease.

Had these experiments been conducted in a large city, or in a populous neighbourhood, some doubts might have been entertained ; but here, where populatiou is thin, and where such an event as a person's having had the small-pox is always faithfully recorded, no risk of inaccuracy in this particular can arise.

Case II.

Sarah Portlock, of this place, was infected with the cow-pox, when a servant at a farmer's in the neighbourhood, twenty-seven years ago.[1]

In the year 1792, conceiving herself, from this circumstance, secure from the infection of the small-pox, she nursed one of her own children who had accidentally caught the disease, but no indisposition ensued. During the time she remained in the infected room, variolous matter was inserted into both her arms, but without any further effect than in the preceding case.

Case III.

John Phillips, a tradesman of this town, had the cow-pox at so early a period as 9 years of age. At the age of 62 I inoculated him, and was very careful in selecting matter in its most active state. It was taken from the arm of a boy just before the commencement of the eruptive fever, and instantly inserted. It very speedily produced a sting-like feel in the part. An efflorescence appeared, which on the fourth day was rather extensive, and some degree of pain and stiffness were felt about the shoulder, but on the fifth day these symptoms began to disappear, and in a day or two after went entirely off, without producing any effect on the system.

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[1] I have purposely selected several cases in which the disease had appeared at a very distant period previous to the experiments made with variolous matter, to show that the change produced in the constitution is not affected by time.

Case IV.

Mary Barge, of Woodford, in this parish, was inoculated with variolous matter in the year 1791. An efflorescence of a palish red colour soon appeared about the parts where the matter was inserted, and spread itself rather extensively, but died away in a few days without producing any variolous symptoms.[1] She has since been repeatedly employed as a nurse to small-pox patients, without experiencing any ill consequences. This woman had the cow-pox when she lived in the service of a farmer in this parish thirty-one years before.

(Eight other cases follow).

Case XIII.

One instance has occurred to me of the system being affected from the matter issuing from the heels of horses, and of its remaining afterwards unsusceptible of the variolous contagion; another, where the small-pox appeared obscurely; and a third, in which its complete existence was positively ascertained.

First, Thomas Pearce, is the son of a smith and farrier near to this place. He never had the cow-pox, but in consequence of dressing horses with sore heels at his father's, when a lad, he had sores on his fingers which suppurated, and which occasioned a pretty severe indisposition. Six years afterwards I inserted variolous matter into his arm repeatedly, without being able to produce anything more than slight inflammation, which appeared very soon after the matter was applied, and afterwards I exposed him to the contagion of the small-pox with as little effect.[2]

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[1] It is remarkable that variolous matter, when the system is disposed to reject it, should excite inflammation on the part to which it is applied more speedily than when it produces the small-pox. Indeed it becomes almost a criterion by which we can determine whether the infection will be received or not. It seems as if a change, which endures through life, had been produced in the action, or disposition to action, in the vessels of the skin; and it is remarkable too, that whether this change has been effected by the small-pox, or the cow-pox, that the disposition to sudden cuticular inflammation is the same on the application of variolous matter.

[2] It is a remarkable fact, and well known to many, that we are frequently foiled in our endeavours to communicate the small-pox by inoculation to black-

Case XV.

Although in the two former instances the system seemed to be secured, or nearly so, from variolous infection, by the absorption of matter from sores produced by the diseased heels of horses, yet the following case decisively proves that this cannot be entirely relied upon, until a disease has been generated by the morbid matter from the horse on the nipple of the cow, and passed through that medium to the human subject.

Mr. Abraham Riddiford, a farmer at Stone in this parish, in consequence of dressing a mare that had sore heels, was affected with very painful sores in both his hands, tumours in each axilla, and severe and general indisposition. A surgeon in the neighbourhood attended him, who, knowing the similarity between the appearance of the sores upon his hands and those produced by the cow-pox, and being acquainted also with the effects of that disease on the human constitution, assured him that he never need to fear the infection of the small-pox; but this assertion proved fallacious, for, on being exposed to the infection upwards of twenty years afterwards, he caught the disease, which took its regular course in a very mild way. There certainly was a difference perceptible, although it is not easy to describe it, in the general appearance of the pustules from that which we commonly see. Other practitioners, who visited the patient at my request, agreed with me in this point, though there was no room left for suspicion as to the reality of the disease, as I inoculated some of his family from the pustules, who had the small-pox, with its usual appearances, in consequence.

Case XVI.

Sarah Nelmes, a dairymaid at a farmer's near this place, was infected with the cow-pox from her master's cows in May, 1796. She received the infection on a part of the hand which had been previously in a slight degree injured by a scratch from a thorn. A large pustulous sore and the usual symptoms

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smiths, who in the country are farriers. They often, as in the above instance, either resist the contagion entirely, or have the disease anomalously. Shall we not be able now to account for this on a rational principle?

accompanying the disease were produced in consequence. The pustule was so expressive of the true character of the cow-pox, as it commonly appears on the hand, that I have given a representation of it in the annexed plate. The two small pustules on the wrists arose also from the application of the virus to some minute abrasions of the cuticle, but the livid tint, if they ever had any, was not conspicuous at the time I saw the patient. The pustule on the forefinger shows the disease in an earlier stage. It did not actually appear on the hand of this young woman, but was taken from that of another, and is annexed for the purpose of representing the malady after it has newly appeared. [See plate in original facing p. 30.]

Case XVII.

The more accurately to observe the progress of the infection, I selected a healthy boy, about 8 years old, for the purpose of inoculation for the cow-pox. The matter was taken from a sore on the hand of a dairymaid, who was infected by her master's cows, and it was inserted on the 14th of May, 1796, into the arm of the boy by means of two superficial incisions, barely penetrating the cutis, each about ½ in. long.

On the seventh day he complained of uneasiness in the axilla, and on the ninth he became a little chilly, lost his appetite, and had a slight headache. During the whole of this day he was perceptibly indisposed and spent the night with some degree of restlessness, but on the day following he was perfectly well.

The appearance of the incisions in their progress to a state of maturation were (*sic*) much the same as when produced in a similar manner by variolous matter.[1] The only difference which I perceived was, in the state of the limpid fluid arising from the action of the virus, which assumed rather a darker hue, and in that of the efflorescence spreading round the incisions, which had more of an erysipelatous look than we commonly perceive when variolous matter has been made use of in the

[1] This appearance was in great measure new to me, and I ever shall recollect the pleasing sensations it excited; as, from its similarity to the pustule produced by variolous inoculation, it incontestably pointed out the close connection between the two diseases, and almost anticipated the result of my future experiments.

same manner ; but the whole died away (leaving on the inoculated parts scabs and subsequent eschars) without giving me or my patient the least trouble.

In order to ascertain whether the boy, after feeling so slight an affection of the system from the cow-pox virus, was secure from the contagion of the small-pox, he was inoculated on the 1st of July following with variolous matter, immediately taken from a pustule. Several slight punctures and incisions were made on both his arms, and the matter was carefully inserted, but no disease followed. The same appearances were observable on the arms as we commonly see when a patient has had variolous matter applied, after having either the cow-pox or the small-pox. Several months afterwards he was again inoculated with variolous matter, but no sensible effect was produced on the constitution.

Here my researches were interrupted till the spring of the year 1798, when from the wetness of the early part of the season many of the farmers' horses in this neighbourhood were affected with sore heels, in consequence of which the cow-pox broke out among several of our dairies, which afforded me an opportunity of making further observations upon this curious disease.

A mare, the property of a person who keeps a dairy in a neighbouring parish, began to have sore heels the latter end of the month of February, 1798, which were occasionally washed by the servant men of the farm, Thomas Virgoe, William Wherret, and William Haynes, who in consequence became affected with sores on their hands, followed by inflamed lymphatic glands in the arms and axillæ, shiverings succeeded by heat, lassitude and general pains in the limbs. A single paroxysm terminated the disease ; for within twenty-four hours they were free from general indisposition, nothing remaining but the sores on their hands. Haynes and Virgoe, who had gone through the small-pox from inoculation, described their feelings as very similar to those which affected them on sickening for that malady. Wherret never had had the small-pox. Haynes was daily employed as one of the milkers at the farm, and the disease began to show itself among the cows about ten days after he first assisted in washing the mare's heels. Their nipples became sore in the usual way, with

bluish pustules, but as remedies were early applied they did not ulcerate to any extent.

(*Six other cases follow.*)

These experiments afforded much satisfaction, they proved that the matter in passing from one human subject to another, through five gradations, lost none of its original properties, J. Barge being the fifth who received the infection successively from William Summers, the boy to whom it was communicated from the cow.

I shall now conclude this inquiry with some general observations on the subject, and on some others which are interwoven with it.

Although I presume it may be unnecessary to produce further testimony in support of my assertion "that the cow-pox protects the human constitution from the infection of the small-pox," yet it affords me considerable satisfaction to say that Lord Somerville, the President of the Board of Agriculture, to whom this paper was shown by Sir Joseph Banks, has found upon inquiry that the statements were confirmed by the concurring testimony of Mr. Dollan, a surgeon, who resides in a dairy country remote from this, in which these observations were made. With respect to the opinion adduced "that the source of infection is a peculiar morbid matter arising in the horse," although I have not been able to prove it from actual experiments conducted immediately under my own eye, yet the evidence I have adduced appears sufficient to establish it.

They who are not in the habit of conducting experiments may not be aware of the coincidence of circumstances necessary for their being managed so as to prove perfectly decisive; nor how often men engaged in professional pursuits are liable to interruptions which disappoint them almost at the instant of their being accomplished; however, I feel no room for hesitation respecting the common origin of the disease, being well convinced that it never appears among the cows (except it can be traced to a cow introduced among the general herd which has been previously infected, or to an infected servant), unless they have been milked by someone who, at the same time, has the care of a horse with diseased heels.

The spring of the year 1797, which I intended particularly to have devoted to the completion of this investigation, proved,

from its dryness, remarkably adverse to my wishes ; for it frequently happens while the farmers' horses are exposed to the cold rains which fall at that season that their heels become diseased, and no cow-pox then appeared in the neighbourhood.

The active quality of the virus from the horses' heels is greatly increased after it has acted on the nipples of the cow, as it rarely happens that the horse affects his dresser with sores, and as rarely that a milkmaid escapes the infection when she milks infected cows. It is most active at the commencement of the disease, even before it has acquired a pus-like appearance ; indeed, I am not confident whether this property in the matter does not entirely cease as soon as it is secreted in the form of pus. I am induced to think it does cease,[1] and that it is the thin, darkish-looking fluid only, oozing from the newly formed cracks in the heels, similar to what sometimes appears from erysipelatous blisters, which gives the disease. Nor am I certain that the nipples of the cows are at all times in a state to receive the infection. The appearance of the disease in the spring and the early part of the summer, when they are disposed to be affected with spontaneous eruptions so much more frequently than at other seasons, induces me to think that the virus from the horse must be received upon them when they are in this state, in order to produce effects ; experiments, however, must determine these points. But it is clear that when the cow-pox virus is once generated that the cows cannot resist the contagion, in whatever state their nipples may chance to be, if they are milked with an infected hand.

Whether the matter, either from the cow or the horse, will affect the sound skin of the human body I cannot positively determine ; probably it will not, unless on those parts where the cuticle is extremely thin, as on the lips, for example. I have known an instance of a poor girl who produced an ulceration on her lip by frequently holding her finger to her mouth to cool the raging of a cow-pox sore by blowing upon it. The hands of the farmers' servants here, from the nature

[1] It is very easy to procure pus from old sores on the heels of horses. This I have often inserted into scratches made with a lancet on the sound nipples of cows, and have seen no other effects from it than simple inflammation.

of their employments, are constantly exposed to those injuries which occasion abrasions of the cuticle, to punctures from thorns and such like accidents, so that they are always in a state to feel the consequences of exposure to infectious matter.[1]

It is singular to observe that the cow-pox virus, although it renders the constitution unsusceptible of the variolous, should, nevertheless, leave it unchanged with respect to its own action. I have already produced an instance[2] to point out this, and shall now corroborate it with another.

Elizabeth Wynne, who had the cow-pox in the year 1759, was inoculated with variolous matter, without effect, in the year 1797, and again caught the cow-pox in the year 1798. When I saw her, which was on the eighth day after she received the infection, I found her affected with general lassitude, shiverings, alternating with heat, coldness of the extremities, and a quick and irregular pulse. These symptoms were preceded by a pain in the axilla. . . . .

It is curious also to observe, that the virus, which with respect to its effects is undetermined and uncertain previously to its passing from the horse through medium of the cow, should then not only become more active, but should invariably and completely possess those specific properties which induce in the human constitution symptoms similar to those of the variolous fever, and effect in it that peculiar change which for ever renders it unsusceptible of the variolous contagion.

May it not then be reasonably conjectured that the source of the small-pox is morbid matter of a peculiar kind, generated by a disease in the horse, and that accidental circumstances may have again and again arisen, still working new changes upon it, until it has acquired the contagious and malignant form under which we now commonly see it making its devastations

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[1] "There seems sufficient reason to think that the infectious matter may be communicated from man to the cow and *vice versâ*, through the absorption which is the inevitable result of the continued friction entailed by the act of milking. It is a subject of daily experience that the absorbent spores in the skin take up solid matter, and it is not likely that they would be closed to fluid." (Note by Jacques Joseph de Laroque, the translator of the French edition of Jenner's writings, published in the year 1800, taken from the excellent work by Dr. Chrestien, entitled, "Opuscule sur l'inoculation de la petite vérole, &c.")

[2] See Case IX. (in original).

amongst us? And, from a consideration of the change which the infectious matter undergoes from producing a disease on the cow, may we not conceive that many contagious diseases now prevalent amongst us, may owe their present appearance, not to a simple, but to a compound origin? For example, is it difficult to imagine that the measles, the scarlet fever, and the ulcerous sore throat with a spotted skin have all sprung from the same source, assuming some variety in their forms according to the nature of their new combinations? The same question will apply respecting the origin of many other contagious diseases, which bear a strong analogy to each other.

There are certainly more forms than one, without considering the common variation between the confluent and distinct, in which the small-pox appears in what is called the natural way.—About seven years ago a species of small-pox spread through many of the towns and villages of this part of Gloucestershire; it was of so mild a nature that a fatal instance was scarcely ever heard of, and consequently so little dreaded by the lower orders of the community, that they scrupled not to hold the same intercourse with each other as if no infectious disease had been present among them. I never saw nor heard of an instance of its being confluent. The most accurate manner, perhaps, in which I can convey an idea of it is, by saying that had fifty individuals been taken promiscuously and infected by exposure to this contagion, they would have had as mild and light a disease as if they had been inoculated with variolous matter in the usual way. The harmless manner in which it showed itself could not arise from any peculiarity either in the season or the weather, for I watched its progress upwards of a year without perceiving any variation in its general appearance. I consider it, then, as a *variety* of the small-pox.[1]

In some of the preceding cases I have noticed the attention that was paid to the state of the variolous matter previous to

[1] My friend, Dr. Hicks, of Bristol, who during the prevalence of this distemper was resident at Gloucester, and Physician to the Hospital there (where it was seen soon after its first appearance in this country), had opportunities of making numerous observations upon it, which it is his intention to communicate to the public.

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the experiment of inserting it into the arms of those who had gone through the cow-pox. This I conceived to be of great importance in conducting these experiments, and were it always properly attended to by those who inoculate for the small-pox, it might prevent much subsequent mischief and confusion. With the view of enforcing so necessary a precaution, I shall take the liberty of digressing so far as to point out some unpleasant facts, relative to mismanagement in this particular, which have fallen under my own observation.

A medical gentleman (now no more), who for many years inoculated in this neighbourhood, frequently preserved the variolous matter intended for his use on a piece of lint or cotton, which, in its fluid state, was put into a vial, corked, and conveyed into a warm pocket ; a situation certainly favourable for speedily producing putrefaction in it. In this state (not unfrequently after it had been taken several days from the pustules) it was inserted into the arms of his patients, and brought on inflammation of the incised parts, swellings of the axillary glands, fever, and sometimes eruptions. But what was this disease ? Certainly not the small-pox ; for the matter, having from putrefaction lost, or suffered a derangement in its specific properties, was no longer capable of producing that malady, those who had been inoculated in this manner being as much subject to the contagion of the small-pox as if they had never been under the influence of this artificial disease ; and many, unfortunately, fell victims to it, who thought themselves in perfect security. The same unfortunate circumstance of giving a disease, supposed to be the small-pox,[1] with inefficacious variolous matter, having occurred under the direction of some other practitioners within my knowledge, and probably from the same incautious method of securing the variolous matter, I avail myself of this opportunity of mentioning what I conceive to be of great importance ; and, as a further cautionary hint, I shall again digress so far as to add another observation on the subject of inoculation.

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[1] " Since the variolar leaven differs in activity in its different stages, it may, in relation to its degree of maturity which changes its energy, affect the part on which it has been deposited too severely or too slightly." (Note by Jacques Joseph de Laroque, from Dr. Chrestien, *op. cit.*)

Whether it be yet ascertained by experiment, that the quantity of variolous matter inserted into the skin makes any difference with respect to the subsequent mildness or violence of the disease, I know not; but I have the strongest reason for supposing that if either the punctures or incisions be made so deep as to go *through* it, and wound the adipose membrane, that the risk of bringing on a violent disease is greatly increased.[1] I have known an inoculator, whose practice was "to cut deep enough (to use his own expression) to see a bit of fat," and there to lodge the matter. The great number of bad cases, independent of inflammations and abscesses on the arms, and the fatality which attended this practice was almost inconceivable; and I cannot account for it on any other principle than that of the matter being placed in this situation instead of the skin.

It was the practice of another, whom I well remember, to pinch up a small portion of the skin on the arms of his patients, and to pass through it a needle, with a thread attached to it previously dipped in variolous matter. The thread was lodged in the perforated parts, and consequently left in contact with the cellular membrane. This practice was attended with the same ill success as the former. Although it is very improbable that any one would now inoculate in this rude way by design,

[1] "Dr. Chrestien (who is as well known owing to his success as a physician as through the various works that he has published, especially that entitled, 'Opuscule sur l'inoculation de la petite vérole et sur la methode d'absorption') states that, in the course of his inoculations, he has observed that the more focci of irritation are established the milder is the small-pox; this, he adds, completely controverts the opinion of many inoculators, who think that the eruption is more abundant in proportion to the larger quantity of matter introduced in the operation. "I should doubtless think as they do," he adds, "if they said that the eruption is bound to increase with the quantity of leaven absorbed without internal irritation, which is capable of counteracting the results of the absorption." Like Chrestien, Girod, Camper and Nicod observed that the inoculation increased in mildness in proportion to the larger number of the punctures, and they attributed this to the more abundant discharge thereby occasioned. It is evidently due to the multiplicity of the centres of irritation. The discharge, when it occurs, takes place only when the eruption and even the suppuration have ceased. By way of illustration it may be mentioned that, in the case of a very large number of inoculated persons, the malady has been confined to fever and severe inflammation of the punctures, without there having been the least discharge from the latter." (Note by Jacques Joseph de Laroque.)

yet these observations may tend to place a double guard over the lancet, when infants, whose skins are comparatively so very thin, fall under the care of the inoculator.

A very respectable friend of mine, Dr. Hardwicke, of Sodbury in this county, inoculated great numbers of patients previous to the introduction of the more modern method of Sutton, and with such success, that a fatal instance occurred as rarely as since that method has been adopted. It was the doctor's practice to make as slight an incision as possible *upon* the skin, and there to lodge a thread saturated with the variolous matter. When his patients became indisposed, agreeably to the custom then prevailing, they were directed to go to bed and were kept moderately warm. Is it not probable, then, that the success of the modern practice may depend more upon the method of invariably depositing the virus in or upon the skin, than on the subsequent treatment of the disease?

I do not mean to insinuate that exposure to cool air, and suffering the patient to drink cold water when hot and thirsty, may not moderate the eruptive symptoms and lessen the number of pustules; yet, to repeat my former observation, I cannot account for the uninterrupted success, or nearly so, of one practitioner, and the wretched state of the patients under the care of another, where, in both instances, the general treatment did not differ essentially, without conceiving it to arise from the different modes of inserting the matter for the purpose of producing the disease. As it is not the identical matter inserted which is absorbed into the constitution, but that which is, by some peculiar process in the animal economy, generated by it, is it not probable that different parts of the human body may prepare or modify the virus differently? Although the skin, for example, adipose membrane, or mucous membranes are all capable of producing the variolous virus by the stimulus given by the particles originally deposited upon them, yet I am induced to conceive that each of these parts is capable of producing some variation in the qualities of the matter previous to its affecting the constitution. What else can constitute the difference between the small-pox when communicated casually or in what has been termed the natural way, or when brought on artificially through the medium of the skin? After all, are the variolous particles, possessing their true specific and con-

tagious principles, ever taken up and conveyed by the lymphatics unchanged into the blood-vessels? I imagine not. Were this the case, should we not find the blood sufficiently loaded with them in some stages of the small-pox to communicate the disease by inserting it under the cuticle, or by spreading it on the surface of an ulcer? Yet experiments have determined the impracticability of its being given in this way; although it has been proved that variolous matter when much diluted with water, and applied to the skin in the usual manner, will produce the disease. But it would be digressing beyond a proper boundary, to go minutely into this subject here.

At what period the cow-pox was first noticed here is not upon record. Our oldest farmers were not unacquainted with it in their earliest days, when it appeared among their farms without any deviation from the phenomena which it now exhibits. Its connection with the small-pox seems to have been unknown to them. Probably the general introduction of inoculation first occasioned the discovery.

Its rise in this country may not have been of very remote date, as the practice of milking cows might formerly have been in the hands of women only; which I believe is the case now in some other dairy countries, and, consequently, that the cows might not in former times have been exposed to the contagious matter brought by the men servants from the heels of horses.[1] Indeed a knowledge of the source of the infection is new in the minds of most of the farmers in this neighbourhood, but has at length produced good consequences; and it seems probable, from the precautions they are now disposed to adopt, that the appearance of the cow-pox here may either be entirely extinguished or become extremely rare.

Should it be asked whether this investigation is a matter of mere curiosity, or whether it tends to any beneficial purpose, I should answer, that, notwithstanding the happy effects of

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[1] I have been informed from respectable authority that in Ireland, although dairies abound in many parts of the Island, the disease is entirely unknown. The reason seems obvious. The business of the dairy is conducted by women only. Were the meanest vassal among the men employed there as a milker at a dairy, he would feel his situation unpleasant beyond all endurance.

inoculation, with all the improvements which the practice has received since its first introduction into this country, it not very frequently produces deformity of the skin and, sometimes under the best management, proves fatal.

These circumstances must naturally create in every instance some degree of painful solicitude for its consequences. But as I have never known fatal effects arise from the cow-pox, even when impressed in the most unfavourable manner, producing extensive inflammations and suppurations on the hands, and as it clearly appears that this disease leaves the constitution in a state of perfect security from the infection of the small-pox, may we not infer that a mode of inoculation may be introduced preferable to that at present adopted, especially among those families, which, from previous circumstances, we may judge to be predisposed to have the disease unfavourably? It is an excess in the number of pustules which we chiefly dread in the small-pox; but in the cow-pox no pustules appear, nor does it seem possible for the contagious matter to produce the disease from effluvia, or by any other means than contact, and that probably not simply between the virus and the cuticle; so that a single individual in a family might at any time receive it without the risk of infecting the rest, or of spreading a distemper that fills a country with terror. Several instances have come under my observation which justify the assertion that the disease cannot be propagated by effluvia. The first boy whom I inoculated with the matter of cow-pox slept in a bed, while the experiment was going forward, with two children who never had gone through either that disease or the small-pox, without infecting either of them.

A young woman who had the cow-pox to a great extent, several sores which maturated having appeared on the hands and wrists, slept in the same bed with a fellow-dairymaid who never had been infected with either the cow-pox or the small-pox, but no indisposition followed.

Another instance has occurred of a young woman on whose hands were several large suppurations from the cow-pox, who was at the same time a daily nurse to an infant, but the complaint was not communicated to the child.

In some other points of view, the inoculation of this disease appears preferable to the variolous inoculation.

In constitutions predisposed to scrofula, how frequently we see the inoculated small-pox rouse into activity that distressful malady! This circumstance does not seem to depend on the manner in which the distemper has shown itself, for it has as frequently happened among those who have had it mildly as when it has appeared in the contrary way.

There are many, who from some peculiarity in the habit, resist the common effects of variolous matter inserted into the skin, and who are, in consequence, haunted through life with the distressing idea of being insecure from subsequent infection. A ready mode of dissipating anxiety originating from such a cause must now appear obvious. And, as we have seen that the constitution may at any time be made to feel the febrile attack of cow-pox, might it not, in many chronic diseases, be introduced into the system, with the probability of affording relief, upon well-known physiological principles?

Although I say the system may at any time be made to feel the febrile attack of cow-pox, yet I have a single instance before me where the virus acted locally only, but it is not in the least probable that the same person would resist the action of both of the cow-pox virus and the variolous.

Elizabeth Sarsenet lived as a dairymaid at Newpark Farm, in this parish. All the cows and the servants employed in milking had the cow-pox, but this woman, though she had several sores on her fingers, felt no tumours in the axillæ nor any general indisposition. On being afterwards casually exposed to variolous infection, she had the small-pox in a mild way. Hannah Pick, another of the dairymaids, who was a fellow-servant with Elizabeth Sarsenet when the distemper broke out at the farm, was at the same time infected; but this young woman had not only sores on her hands, but felt herself also much indisposed for a day or two. After this I made several attempts to give her the small-pox by inoculation, but they all proved fruitless. From the former case, then, we see that the animal economy is subject to the same laws in one disease as the other.

The following case which has very lately occurred, renders it highly probable that not only the heels of the horse, but other parts of the body of that animal, are capable of generating the virus which produces the cow-pox.

An extensive inflammation of erysipelatous kind, appeared without any apparent cause upon the upper part of the thigh of a sucking colt, the property of Mr. Millet, a farmer at Rockhampton, a village near Berkeley. The inflammation continued several weeks, and at length terminated in the formation of three or four small abscesses. The inflamed parts were fomented, and dressings were applied by some of the same persons who were employed in milking the cows. The number of cows milked was twenty-four, and the whole of them had the cow-pox. The milkers, consisting of the farmer's wife, a man and a maidservant, were infected by the cows. The manservant had previously gone through the small-pox, and felt but little of the cow-pox. The servant maid had some years before been infected with the cow-pox, and she also felt it now in a slight degree. But the farmer's wife, who had never gone through either of these diseases, felt its effects very severely.

That the disease produced upon the cows by the colt, and from thence conveyed to those who milked them, was the *true* and not the *spurious* cow-pox, there can scarcely be any room for suspicion ; yet it would have been more completely satisfactory had the effects of variolous matter been ascertained on the farmer's wife, but there was a peculiarity in her situation which prevented my making the experiment.

Thus far have I proceeded in an inquiry, founded, as it must appear, on the basis of experiment ; in which, however, conjecture has been occasionally admitted in order to present to persons well situated for such discussions, objects for a more minute investigation. In the meantime I shall myself continue to prosecute this inquiry, encouraged by the hope of its becoming essentially beneficial to mankind.